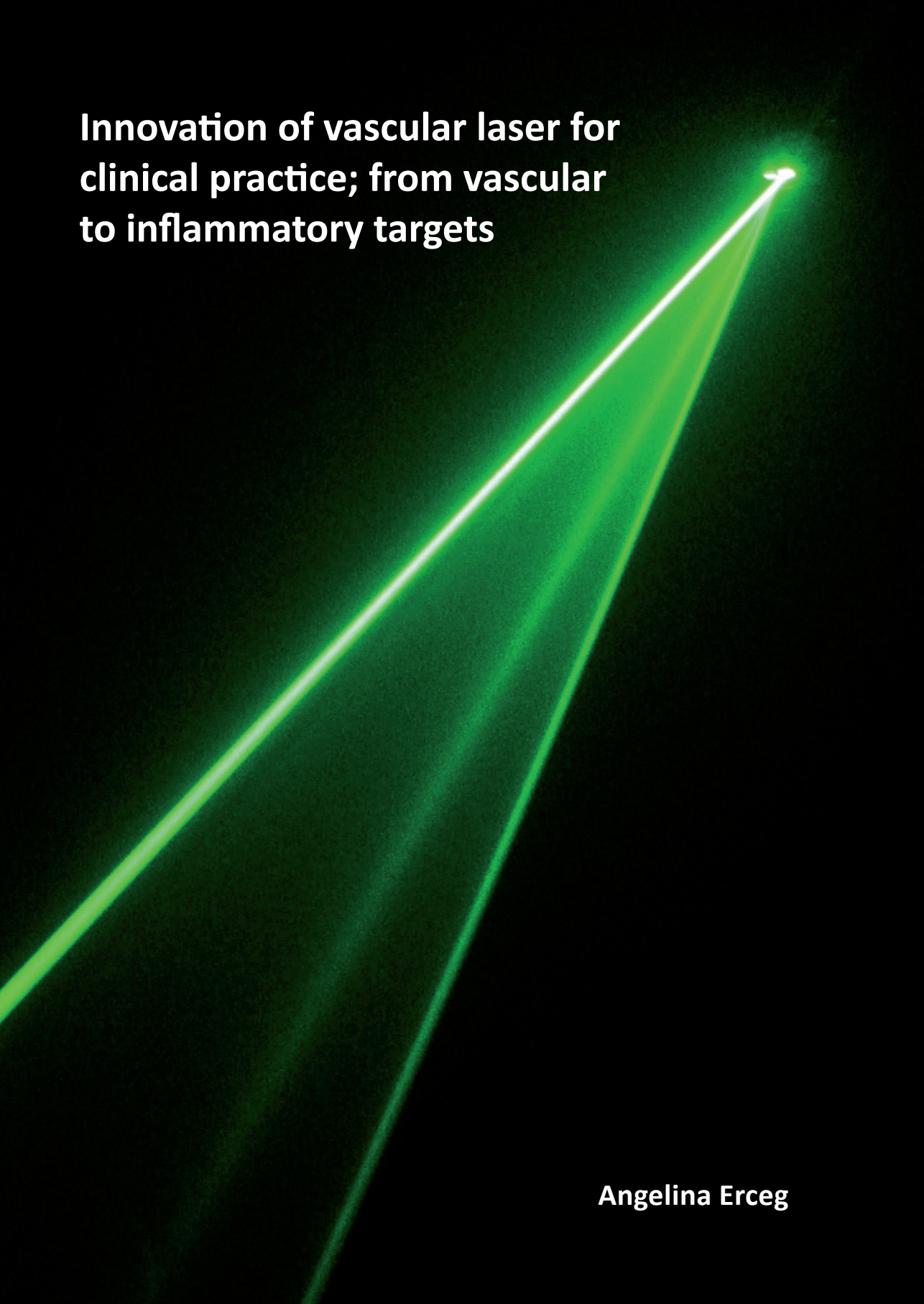
Innovation of vascular laser for clinical practice; from vascular to inflammatory targets



Angelina Erceg

Innovation of vascular laser for clinical practice; from vascular to inflammatory targets

Angelina Erceg

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Innovation of vascular laser for clinical practice; from vascular to inflammatory targets

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Medische Wetenschappen

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"It is never too late to be what you might have been."

George Eliot (1818-1880)

Voor mijn allerliefsten

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Abbreviations

AEC	3-amino-9-ethylcarbazole
ANOVA	Analysis of variance
APTD	Argon pumped tunable dye
CB	Calcipotriol/betamethasone dipropionate ointment
CD2	Receptor expressed on all Tcells and most NK cells, upregulated on activated T-cells
CD3	Pan T-cell marker
CD4	Marker for helper T-cells
CD25	Early T-cell activation antigen: α-subunit of the IL-2 receptor
CD45RO	Marker for memory effector T cells
CD45RA	Marker for naive T cells
CD94	Inhibitory receptor expressed on NK cells and some NK-T cells
CD161	Obligatory activating NK-T cell receptor
CLASI	Cutaneous lupus erythematosus disease area and severity index
CO_2	Carbon dioxide
CW	Continuous wave
DLE-PS	Discoid lupus erythematosus photo score
DLE-SS	Discoid lupus erythematosus skin score
EC	Electrocoagulation
ECR	Estimated clearance rate
ESS	Eczema severity score
GITR	Glucocorticoid-induced tumor necrosis factor receptor, inhibitory on regulatory T cells
HE	Hematoxylin and eosin staining
HRP	Horse radish peroxidase
J/cm^2	Joule/square centimeter
Ki67	Marker for cycling epidermal cells
K10	Epidermal marker for differentiation
KTP	Potassium titanyl phosphate
LASER	Light amplification by stimulated emission of radiation
LED	Light emitting diode
LOE	Level of evidence
LT	Lupus tumidus
ms	Millisecond
NAPSI	Nail psoriasis severity index
Nd:YAG	Neodymium-doped yttrium aluminium garnet

nm	Nanometer
PASI	Psoriasis area and severity index
PBS	Phosphate buffered saline
PDL	Pulsed dye laser
PGA	Physician's global assessment
PSI	Psoriasis severity index
ROI	Region of interest
SA	Salicylic acid
SCLE	Subacute cutaneous lupus erythematodes
SEM	Standard error of the mean
SLE	Systemic lupus erythematosus
SN	Spider nevus
SUM	Psoriatic plaque severity score
TRT	Thermal relaxation time
VAS	Visual analogue scale
W	Watt
µm	Micrometer
µs	Microseconds

General introduction 1

General introduction

This thesis explores the value of pulsed dye laser in the treatment of inflammatory skin diseases, in particular psoriasis and cutaneous discoid lupus erythematosus (CDLE). This work is inspired by the well established effect in vascular lesions and the evidence of involvement of the microvasculature in inflammatory dermatoses. In this introduction we will highlight the current knowledge on laser therapy, describe the clinical aspects of these diseases and finally we will define the aims of this thesis.

1.1 Laser therapy

1.1.1 History

The term LASER is an acronym for *L*ight *A*mplification by *S*timulated *E*mission of *R*adiation. The concept of stimulated light emission was introduced by Einstein in 1917.[1] He proposed that a photon of electromagnetic energy is able to stimulate the emission of another identical photon from atoms or molecules that are in an excited state. Based on this theory, Maiman developed more than forty years later, in 1960, the first laser by using a ruby crystal to produce red light with a wavelength of 694 nm.[2] In 1963, Goldman became the first physician to utilize a laser on humans, initiating dermatologic application of laser technology.[3,4] He applied the ruby laser for a variety of cutaneous pathologies. During the next two decades the development of the argon and carbon dioxide (CO_2) lasers soon followed and served as the focus of cutaneous laser research.[5,6] The argon laser emits blue-green light (wavelengths 488 and 514 nm) and was initially used to treat congenital vascular lesions. Although this treatment showed an effective lightning in most hemangiomas and port-wine-stains, hypertrophic scar formation was frequently seen as a side effect.[5,7,8] The CO_2 laser, emitting infrared light at 10,600 nm, was used for tissue vaporization and destruction of different epidermal and dermal lesions.[5,9] The prolonged tissue exposure to laser energy resulted in excessive thermal injury of the skin, what unfortunately often led to side effects as hypertrophic scarring and pigmentary changes. Anderson en Parrish brought a revolution to the cutaneous laser surgery by introducing the theory of selective photothermolysis in 1983.[10] This theory describes specific destruction of a target in the skin with minimal thermal injury, providing a more selective approach with less collateral damage. In the years following this discovery till now, greater understanding of the complex laser-tissue interaction in combination with extensive advances in laser technology have brought cutaneous laser surgery to the point that it is now: the golden standard for the treatment of many congenital and acquired conditions.[5, 11]

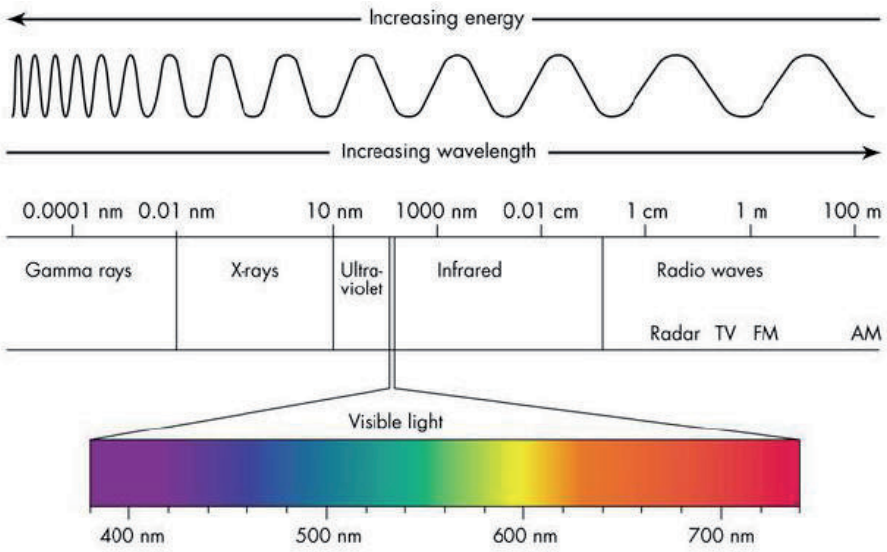

Figure 1. The electromagnetic spectrum.

1.1.2 Physical principles[5,12]

For a detailed review on physical principles the reader is referred to a review by Ratz *et al.*[5] In the electromagnetic spectrum (figure 1), light is one portion that exhibits properties of photons and waves. Photons of light are like small packages, each having a specific wavelength that serves as the "stuff" inside the package. The wavelength is responsible for the colour of visible light. Wavelengths of visible light range from approximately 400 nm (violet) to approximately 750 nm (red). Ultraviolet light has much shorter (10-400 nm) wavelengths, whereas infrared light has much longer (750-1,000,000+ nm) wavelengths. Regardless of colour or wavelength, the speed of light is constant at 299,792,458 m/s. This speed is constant per unit of time, so the frequency (the number of wavelengths within a unit of time) will be high for short wavelengths and low for long wavelengths. Each atom or molecule has a natural tendency to exist in its natural or resting state, with its outer orbiting electron in a stable position. By absorbing a photon of energy, the outer orbiting electron is moved into the next orbital level, which is an unstable condition. Its natural tendency will be to drop back to its normal or resting state and releasing a characteristic photon of energy, called *spontaneous emission*. When many atoms or molecules undergo spontaneous decay, the emission will be out of phase with one another. However, if a photon of enough energy stimulates an electron in its excited state, that photon will cause orbital decay of the electron, sending the electron back to its resting state, resulting in

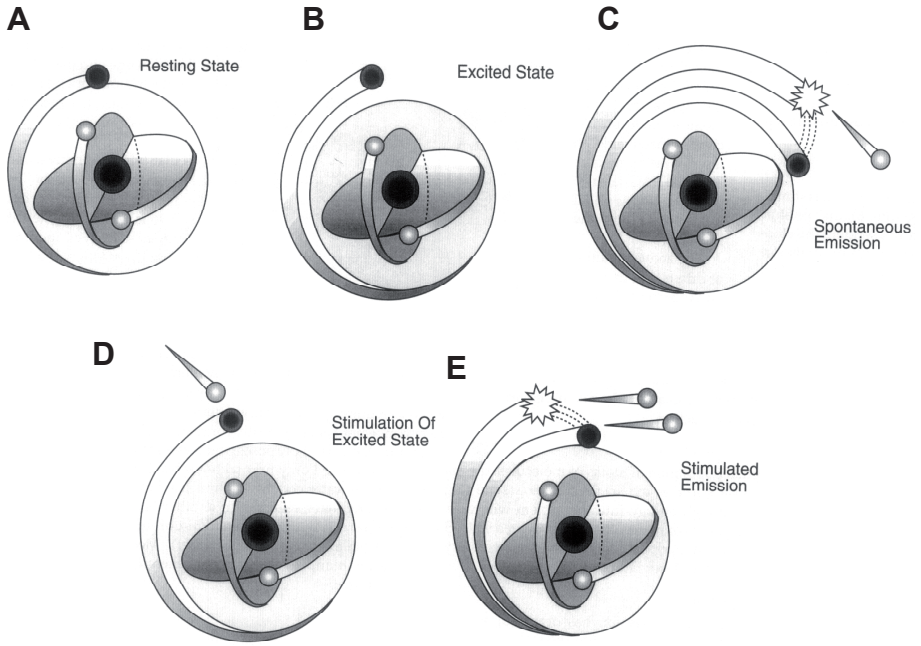

Figure 2. Resting state of atom or molecule (2A), after absorbing a photon of energy the outer orbiting electron is moved to the next level (2B); without further power the unstable electron falls back releasing energy (2C); further absorption energy results in stimulation of excited-state atom or molecule (2D). Stimulation of the excited-state atom or molecule results in falling back of the stimulated electron and emission of two identical photons travelling in the same direction (2E).

the emission of a second photon identical to the incident photon. So, two photons of equal wavelength (colour) are released from the atom, and those two photons are travelling in the same direction and are in phase both spacially and temporally. This process, called *stimulated emission*, is the first necessary element in the production of laser light (figure 2). Normally, atoms or molecules contain a much greater number of particles in their resting state. Pumping enough energy into the system, more atoms or molecules are transformed into their excited states. This change, called *population inversion*, is necessary for the production of laser light. If energy is still being pumped into the system, after population inversion has occurred, the stimulated emission of in-phase photons will result in their impact on other excited-state electrons, which results in additional in-phase photons that will do the same thing, namely produce more in-phase photons. In the optical resonator of the laser, this chain-reaction “mass production” of in-phase photons is further magnified, resulting in light amplification (figure 3).

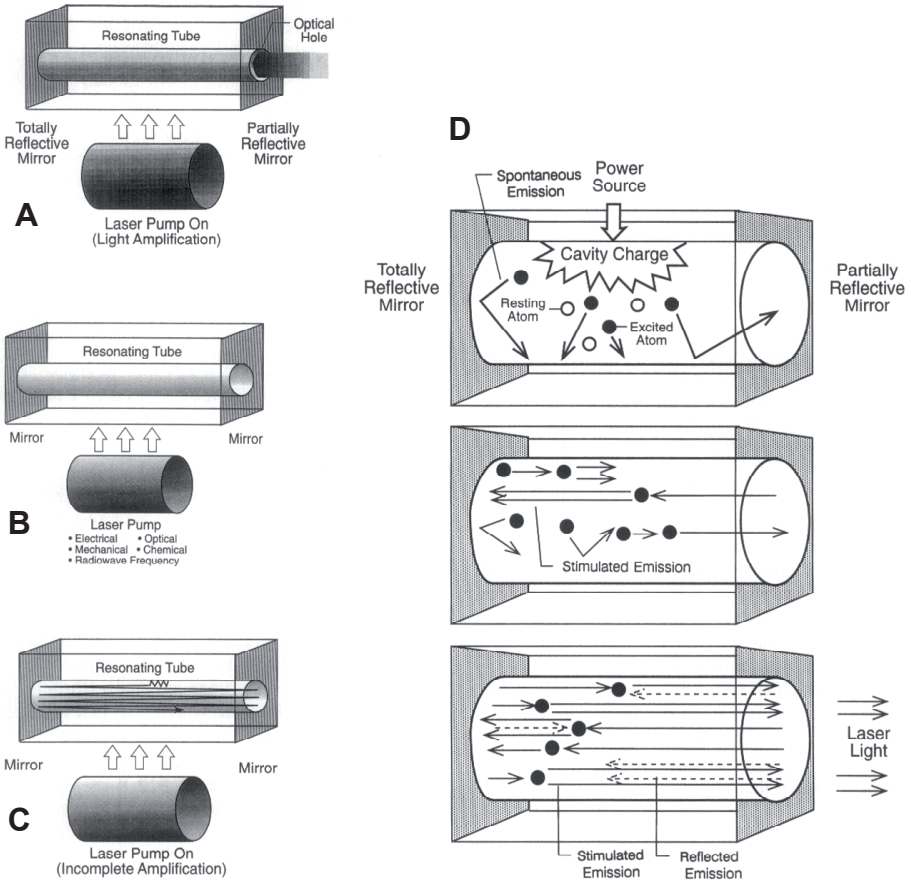

Figure 3. Basic laser Construction (A), external power is introduced to the laser (B), production of laser light (C), laser light entering the laser delivery system (D).

1.1.3 Laser design and properties of laser light[12]

Basically the design of every laser is the same (figure 3). It consists of three basic parts:

1. An optical cavity or resonator.
2. An active medium with a suitable set of energy level to support laser action.
3. A source of pumping energy.

Ad 1. The optical cavity, also called (optical) resonator, chamber or laser cavity, can be thought of as an elongated box with a “hole” in one end. At the end of the box is a fully reflective mirror and at the opposite end a partially reflective mirror, which allows for transmission of only a very small amount of light.

Ad 2. The optical cavity contains a medium which can be solid (crystal), liquid (rhodamine dye dissolved in organic solvent), a gas or a mixture of gases (argon,

carbon dioxide, copper vapour, xenon chloride etc). The medium becomes an active medium when it is energized into its excited state by a power source. Lasers are named according to their medium.
Ad 3. The pumping energy can be derived from different sources including electricity, radio-frequency enhancement, light, chemical reaction and mechanical power. Most medical lasers are pumped by electrical or optical energy or by radio-frequency enhancement.
When external power is introduced to the laser, atoms are elevated to their excited state and a population inversion occurs. The resulting photons released are all identical and are reflected back and forth between the mirrors at each end of the optical cavity. Continued absorption of energy results in further stimulated emission and ultimately in light amplification and the production of laser light. This light enters the laser delivery system, which for most lasers is quartz fibre optics.
Laser light has some key properties that distinguish it from other light sources and which are the basis for the therapeutic application. These properties are:
Monochromacity: The specific wavelength of laser light influences the distance it can penetrate into the tissue. The depth of the penetration generally increases with increasing wavelength within the spectrum of visible light
Coherence: The waves of light are in phase with each other in both time and space. The light emitted from a laser is in the same direction and in the same phase.
Collimation: A laser creates a collimated beam by reflecting the light between the two mirrors in the optical cavity, that allows the exit of parallel waves only. The tendency toward divergence is low because the waves of light are parallel to each other.
High power: The amplification process within the optical cavity produces a high power density. Some lasers are capable of the continuous discharge of light, called continuous wave (CW), whereas others seem to build up power before releasing their pulse of relatively high power (pulsed lasers). Duration and power of the pulse can be varied. The output of continuous wave lasers is measured as power in watts (W), for pulsed lasers output is measured as energy in joules (J) taking the pulse duration in account. Irradiance, the power density of a laser beam, refers to laser power per unit area and takes the spot size (area of laser beam= $\pi.r^2$) in account (W/cm^2). Energy density or fluence is defined as the irradiance multiplied by exposure time (J/cm^2). Fluence and irradiance are directly proportional to each other:

$$\text{Fluence } (J/cm^2) = \text{irradiance } (W/cm^2) \times \text{exposure time } (s)$$

1.1.4 Laser-tissue interaction[5,13,14]

After a beam of light strikes the skin, 4-7% is reflected because of the difference in the refractive indices of air and stratum corneum. The remaining 93-96% enters the skin, where it is scattered, transmitted or absorbed. Scattering occurs when

particles within the skin spread the incoming beam of light in all directions, limiting its depth of penetration. Light is transmitted when it passes through the tissue unaltered. In general, only when light is absorbed, tissue effects can occur: the photon surrenders its energy to an absorbing molecule, called chromophore. The amount of absorption is determined by the chromophore present in the skin and whether a wavelength that corresponds to the absorptive characteristics of that chromophore is used. The principal endogenous chromophores of the skin are water, melanin and haemoglobin, whereas tattoo ink is an example of an exogenous chromophore. Once laser energy has been absorbed in the skin photochemical, photomechanical or photothermal effects may occur; destruction of the target results from the conversion of absorbed energy into heat. *Photochemical effects* result from the native or photo sensitizer related reactions, de facto the principle of photodynamic therapy. *Photomechanical effects* result from acoustic waves induced by the extremely rapid thermal expansion, causing destruction of the absorbing tissue. *Photothermal effects* occur when a chromophore absorbs the corresponding wavelength of energy.

1.1.5 Selective photothermolysis[5,10,14,15]

In dermatology, the ultimate aim of the use of lasers is to direct energy selectively at a specific chromophore, without collateral damage to the adjacent tissues. This is the principle of selective photothermolysis.

In order to reach selectivity, the beam of light produced by the laser must have a wavelength preferentially absorbed by the targeted chromophore in the lesion, the fluence must be sufficiently high to generate enough energy to thermally alter the target tissue and the pulse duration must be shorter than the thermal relaxation time (TRT) of the chromophore to prevent spread of thermal energy beyond the targeted chromophore. The TRT is the time required by the chromophore to cool down to half of its peak temperature after laser irradiation and is proportional to the square of the size of the chromophore. In general, small objects have a shorter TRT than large ones; melanosomes of 0.5-1.0 μm cool faster than capillaries measuring 10-100 μm. If the pulse width exceeds or equals the TRT, the heat diffusion to surrounding tissues leads to unnecessary thermal damage. Finally, the energy delivered to the chromophore must by high enough to destroy it, within the pulse duration. So, by fine-tuning the wavelength, the pulse duration and the fluence, a laser can be tailored to provide selective damage to the lesions without non specific thermal damage to the skin.

1.1.6 Vascular lasers[5,16]

Vascular laser systems target intravascular oxyhemoglobin. The three primary absorption peaks for oxyhaemoglobin are within the visible range of the

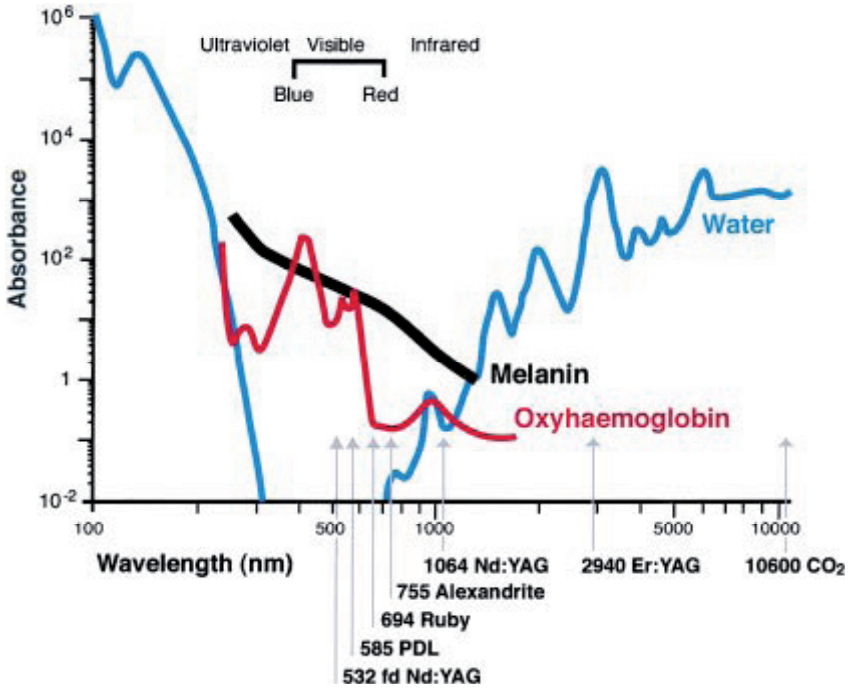

Figure 4. Absorption spectra. Note the heterogeneous absorption spectra of chromophores. (modified from Acland KM and Barlow RJ. Lasers for the dermatologist. Br J Dermatol 2000 Aug;143(2):244-55)

electromagnetic spectrum: 418, 542 and 577 nm (figure 4). The dominant absorption peak is 418 nm, but this wavelength only penetrates into the dermal-epidermal junction (100 µm), which restricts the use of a laser with this wavelength for cutaneous vascular lesions. Lasers that have been used to treat vascular lesions include argon laser (488/514 nm), argon pumped tunable dye (APTD) (577/585 nm), potassium titanyl phosphate (KTP) (532 nm), krypton (568 nm), copper vapour/bromide (578 nm), pulsed dye laser (PDL) (585/590/595/600 nm), long pulsed alexandite laser (755 nm), diode laser (800 nm), neodymium-doped yttrium aluminium garnet (Nd:YAG) (532/1064 nm).

The argon laser produces nonspecific thermal injury resulting from exposure intervals exceeding the thermal relaxation time of the vessels, so increasing the risk of scarring and dyspigmentation. The APTD, krypton, copper vapour/bromide and KTP lasers are continuous wave (CW) that can be mechanically shuttered to deliver pulses as short as 20 ns called quasi-CW. Unfortunately this quasi-CW nature is often associated with higher incidences of hypertrophic scarring and textural changes. The KTP laser uses a Nd:YAG crystal (1064 nm) to produce light that is passed through a KTP crystal that frequency doubles the wavelength to 532 nm. Good results have

been reported by several investigators, after treatment of facial teleangiectasias with this device. Compared with longer wavelength vascular-specific lasers, potential limitations of the 532 nm wavelength include decreased tissue penetration of its shorter wavelength resulting in diminished absorption by deeper vessels. In addition, the 532 nm wavelength is more avidly absorbed by melanin than the 585/595 nm wavelength of the PDL, thereby limiting its use for patients with darker skin types.

The flashlamp-pumped PDL was the first laser developed specifically for the treatment of vascular lesions based on the principles of selective photothermolysis. It uses a high power flashlamp to energize an organic dye (rhodamine) and produce a true pulse of yellow light. Although original investigators used a 577 nm system, the wavelength was modified to 585 nm and more later to 595 nm and 600 nm, to effect a deeper tissue penetration, while maintaining vascular specificity. Also the pulse duration has been prolonged from 0.45 ms up to 40 ms, so vessels could be heated more slowly, producing less profound and shorter lasting purpura. Also, dynamic cooling devices were incorporated to reduce discomfort during treatment and postoperative occurrence of epidermal damage and pigmentary change.

The pulsed dye laser is considered to be the treatment of choice for many vascular lesions.[11] The efficacy of PDL in vascular lesions has been thoroughly investigated. Its application has been expanded to treatment of other skin conditions such as inflammatory skin diseases, currently addressed in this thesis. The efficacy and position of the PDL in these inflammatory skin diseases has only sparsely been explored, and is addressed in this thesis.

1.2 Psoriasis

1.2.1 Epidemiology

Psoriasis is a chronic relapsing non-infectious inflammatory skin disorder, which affects approximately 1-3 % of the Caucasian population.[17,18] The highest prevalence is seen in European and North American Caucasians. The disease is uncommon in Afro-Americans and almost non-existent in Native Americans.[18] Man and women are equally affected.[19] The disease may occur at any age although two peak incidences have been reported: a peak between 16 and 22 years and a later one at 57-60 years, the late onset type.[20]

Genetic disposition seems to play an important role in the susceptibility to develop psoriasis. Population studies have shown that the incidence is greater in first and second degree relatives of psoriasis patients than in the general population. There is evidence that multiple genes are involved and this had led to the identification of different psoriasis-susceptibility loci.[21,22]

1.2.2 Clinical presentation

Psoriasis is a skin disease with a variable morphology, severity, distribution and course.

The commonest type of psoriasis is *chronic plaque psoriasis* (*psoriasis vulgaris*), which accounts for approximately 90 % of all cases. It is characterized by often symmetrically distributed, sharply demarcated, erythematosquamous plaques of varying size with predilection sites on the dorsal sites of the elbows, knees and on the scalp and sacral region. The scales of these lesions are typically silvery white and scratching these looks like scratching on a wax candle ("signe de tache de bougie").[23]

Guttate psoriasis (*psoriasis guttata*) is the acute onset of droplet-like lesions disseminated over the body. Classically, it occurs after an acute group B haemolytic streptococcal infection or viral infection of the pharynx or tonsillitis and often clears in a few weeks to months.[23]

Various forms of pustular psoriasis have been described. Generalized pustular psoriasis (Von Zumbusch psoriasis) is characterized by disseminated deep-red erythematous areas and pustules, which may merge to extensive lakes of pus. Localized forms include palmoplantar pustulosis (morbus Andrews-Barber) and acrodermatitis continua of Hallopeau, consisting of yellow-brown, sterile pustules on a background of erythema and scaling affecting the palms and/or soles.[23]

Both pustular and the erythematosquamous forms may progress to psoriatic erythroderma, which can lead to hypothermia, hypoalbuminaemia and high output cardiac failure eventually rendering it as a possible life-threatening condition.

Extracutaneous manifestations of psoriasis are nail psoriasis (psoriasis unguium) and psoriatic arthritis (psoriasis arthropatica). Nail involvement is present in 25-50% of all

Figure 5. Clinical picture of recalcitrant plaque psoriasis localized on the elbow.

types of psoriasis and is more frequently seen with psoriatic arthropathy. The most common changes seen in nails are pitting, discoloration (oil drop phenomenon), subungual hyperkeratosis and onycholysis. Psoriatic arthritis occurs in about 5-10% of patients with psoriasis.
The studies in this thesis have been focused on plaque psoriasis, especially solitary recalcitrant lesions.

1.2.3 Clinical course and triggering factors

The course of psoriasis is unpredictable, but is usually chronic with exacerbations and remissions. It is a multifactorial disease caused by the interaction between genes and environmental triggering factors. Genetic predisposition is apparent and has been confirmed in twin studies, which have been reviewed in 1997.[24]
Triggering factors have been reported to play a role in the initiation of the disease process and exacerbation of pre-existing disease. These are trauma (Koebner phenomenon),[25] infections (particular streptococcal infections of the upper respiratory tract), drugs (β-blokkers, lithium, anti-malarials, non-steroidal anti-inflammatory agents),[26] psychogenic stress,[27] increased alcohol consumption, obesity, smoking and HIV.[26,28] Repeated traumata at friction sites or combination of itching conditions (neurodermatitis or prurigo) with psoriasis can be a trigger yielding into solitary recalcitrant lesions.

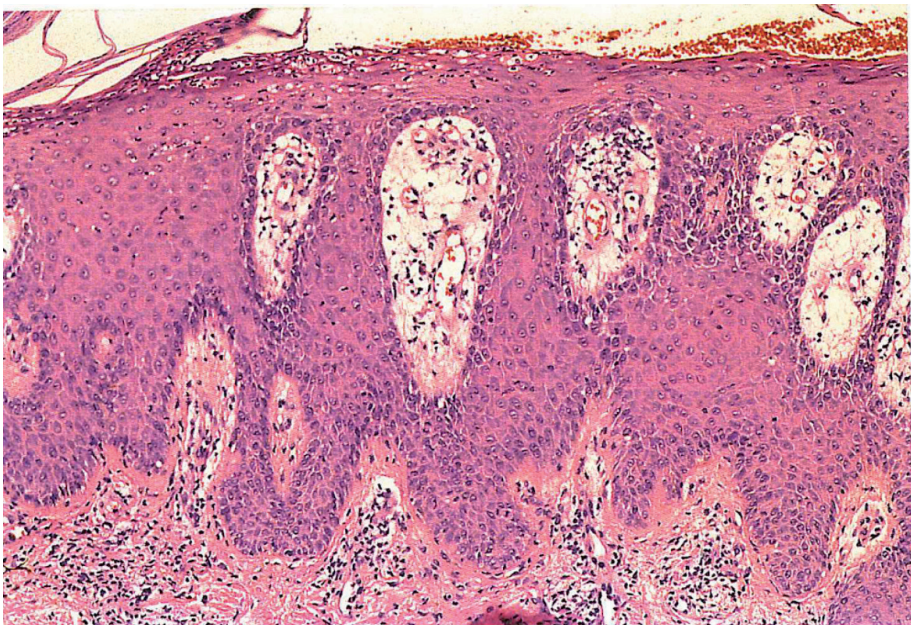

Figure 6. Classical histopathological picture of psoriasis with the characteristic epidermal and inflammatory abnormalities; note the robust dermal papillae with the increased microvasculature and the thinning of the suprapapillary plate.

1.2.4 Histopathology[23]

In general, psoriasis has three main histopathologic features:

1. Epidermal hyperplasia with epidermal thickening.
2. An inflammatory infiltrate of mainly T-cells, predominantly intra-dermal.
3. Dilated, elongated and increased prominent superficial capillaries in the dermis.

The histopathologic findings can vary with the age of the lesions.[29]

1.2.5 Treatments of psoriasis

A spectrum of treatments is available for the management of patients with psoriasis. The majority of patients is treated with a topical treatment such as vitamin D,[30] corticosteroids,[31-33] or calcineurin inhibitors.[34] Classical topical treatments such as dithranol[35] and tar[36] are provided at day care centres and these options may be indicated as second line topicals. Photo(chemo)therapy,[37] classical systemic treatments such as methotrexate,[41,42] fumarates,[38-40] retinoids[43] and cyclosporine[44] are indicated if the condition is too wide spread and or in situations that topical treatments are not effective enough or not practical. The next level of treatment are biologics (anti-TNF treatments and anti-p40 IL12/23) for those patients who cannot be controlled adequately on the previously mentioned options.[45,46] One manifestation represents major difficulties in the management of psoriasis: solitary chronic recalcitrant lesions.

Figure 7. Recalcitrant plaque psoriasis devided in four parts; each consecutive part was treated once with fluences 5.5, 6.5, 7.5 and 8.5 J/cm^2, using the same spot size. Note the marked improvement for the section treated with 8.5 J/cm^2.

These lesions remain after intensified topical and systemic treatment and can be the reason for prolonged treatment and high cumulative toxicity resulting from dose-increments of treatments. Solitary recalcitrant plaques are an unmet need in the management of psoriasis.

Most treatments focus on the inflammatory changes and/or epidermal changes in psoriasis. An option which has not been explored sufficiently in the past is the endothelial changes in psoriasis as a potential anti-psoriatic target. Therapies which focus on the alteration in the capillaries have been neglected as a possible therapeutic target, although several reports mentioned an increase in the dermal papillary vasculature as one of the earliest observable changes in a new psoriatic lesion.[47-50] The clinical improvement during treatment is preceded by micro-vascular improvement, indicating that the expanded superficial micro-vasculature bed of psoriatic skin is an essential component, which maintains clinical lesions. Due to these observations, the hypothesis is, that selective destruction of the dilated papillary vessels in psoriasis by selective photothermolysis, may reduce the transmigration of inflammatory cells, and so clearing psoriasis plaques. Several studies reported partial and total clearance of psoriasis after PDL treatment.[51-57] In this thesis the efficacy and safety of PDL treatment in recalcitrant plaque psoriasis is studied and compared and contrasted with established therapy.

1.3 Chronic discoid lupus erythematosus

1.3.1 Epidemiology[58-62]

Chronic discoid lupus erythematosus (CDLE), is one of the three major forms of lupus erythematosus (LE). This is a spectrum of diseases with variation in course and prognosis. There is an overlap in clinical, histological and laboratory findings which may change during the course of the disease making the distinctions difficult. The other two major forms are subacute cutaneous lupus erythematosus (SCLE) and systemic lupus erythematosus (SLE).

CDLE is the most common form of cutaneous lupus. Women are more affected than men with a ratio ranging from 2:1 to 4:1. The risk of a patient with CDLE developing overt SLE is between 1.3 and 5%. The disease typically affects young patients, with an onset between 20 and 40 years. It has been proposed that genetic factors and somatic mutations are implicated in the pathogenesis of the disease

1.3.2 Clinical presentation[58-62]

Each CDLE lesion is characterized by well defined, erythematous scaly patches, which tend to heal with scarring, atrophy and pigmentary changes. The lesions start with persistent indurated erythematous papules and plaques, centrally covered by a firmly adherent white scale. If the scale is removed, hyperkeratotic spicules can been seen, representing follicular plugs (carpet tack sign). While evolving, the periphery is typically raised and erythematous, while the centre gradually becomes atrophic. There are pigmentary changes as well, showing hypo- or depigmentation in black skin, and hyperpigmentation and teleangiectases in white skin. The face is most commonly affected, and the scalp, ears, nose, arms, legs and trunk to a lesser extent. Alopecia occurs in the scalp lesions in approximately one-third of patients and is usually permanent. CDLE can be either localized or disseminated. The course of CDLE is difficult to predict. Each patient with newly diagnosed CDLE should be evaluated for signs of SLE. If these are negative, then one can diagnose CDLE as LE limited to the skin. The onset of lesions may be precipitated by a variety of factors, including trauma, mental stress, sunburn, infection, exposure to cold and pregnancy. Occasionally, drugs may precipitate lesions of CDLE. Once lesions have developed, exacerbations may be triggered by a variety of factors, like sun exposure, cold, hormonal changes and mental stress.

1.3.3 Histopathology[59,60]

The epidermis is usually atrophic with follicular plugging. The basilar keratinocytes show vacuolar degeneration, while the microscopic basement membrane zone is more prominent and thickened. In the dermis there are lymphocytic infiltrates around the vessels and adnexal structures, and scattered diffusely. Perifollicular infiltrates are

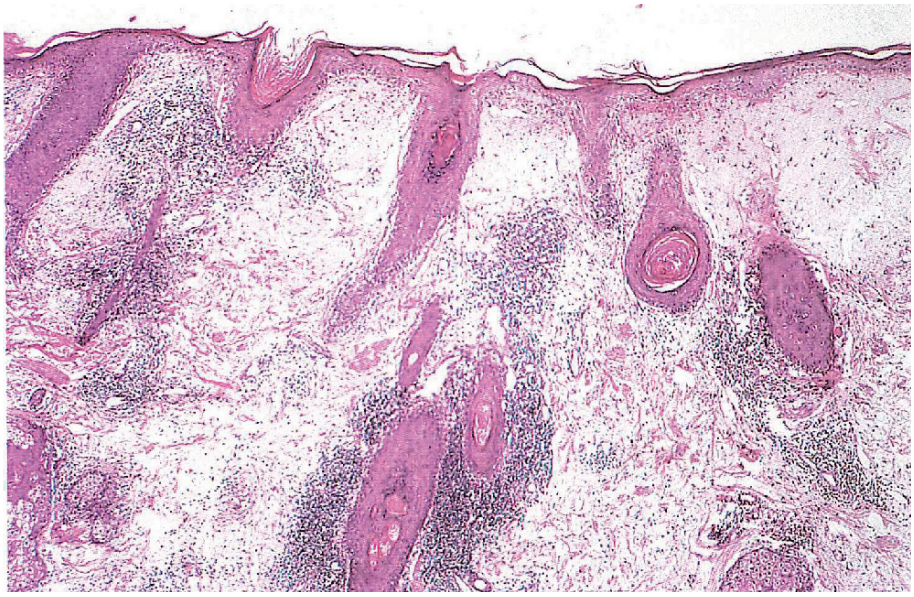

Figure 8. Histology of chronic discoid lupus erythematosus.

especially common. In addition, mucin is common, as are telangiectases. Collagen and elastic fibres are both damaged. The infiltrate can extend to the subcutaneous fat, where typically there is both lobar and septal involvement. Immunoglobulins IgG, IgA, IgM and complement can be observed in approximately 80% of the patients at the dermal-epidermal junction in skin lesions present for six weeks or more.

1.3.4 Treatment of CDLE

CDLE can be treated with different therapies, as monotherapy or in combination therapy. In general topical agents, systemic medication and physical/surgical therapies are treatment options.

Topical therapies commonly used for CDLE includes high potent corticosteroids,[62-64] sunscreens[65] and calcineurin inhibitors,[76,77] whereas systemic therapies includes antimalarial agents[66-67], glucocorticosteroids,[58,59] retinoids,[68,69] dapson,[70] methotrexate,[71] thalidomide,[72] immunoglobulins,[73] azathioprine,[74] cyclophosphamid,[75] biologicals,[78,79] cyclosporine,[80] immunoglobulins,[81] mycophenolate mofetil,[82] rituximab[83] and anti-TNFα agents.[84]

Physical and surgical therapies are indicated, when the topical and systemic treatments lack efficacy or show/predict (serious) adverse events. Physical and surgical therapies includes cryotherapy,[58,59]dermabrasion[58,59] and laser treatment,[85-90] preferentially with the pulsed dye laser. The development of laser therapy for recalcitrant lesions in CDLE may provide an important innovation for better care for these patients.

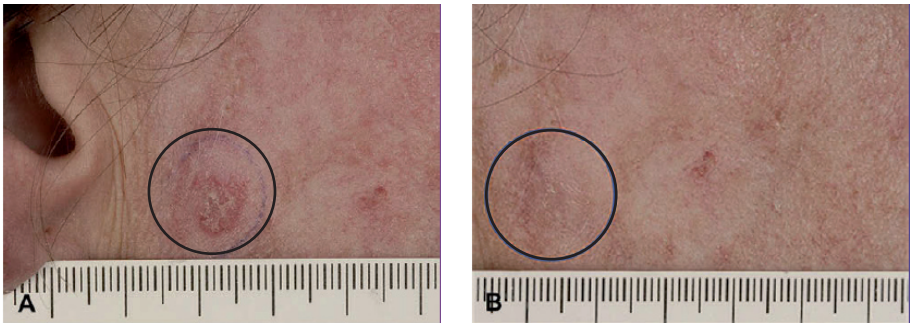

Figure 9. CDLE lesion on the right cheek before PDL treatment (A) Almost total clearance of CDLE lesion right cheek after laser treatment (B).

Concerning the role of the PDL in the modulation of the inflammatory response of CDLE, it has been observed that the endothelial cell activation plays an important role in the pathogenesis of lupus.[89,90] This role could be due to the fact that higher levels of adhesion molecules on the surface of the endothelial cell, such as E-selectine, are correlated with active disease in LE patients. The hypothesis is that the selective destruction or coagulation leads to a modulation of the inflammatory network.[89,90]
In order to find out whether a new treatment provides a significant innovation, objective and reproducible disease assessment is needed. So, to monitor the clinical effects of pulsed dye laser therapy, the objective determination of the skin lesion status is necessary. The cutaneous lupus erythematosus disease area and severity index (CLASI)[91] is an important instrument for disease severity assessment. In brief, this instrument has separate scores for activity and damage of CDLE lesions at 13 anatomic sites. It is an extensive instrument and not focused on one single lesion.

1.4 Aims of this thesis

In chronic therapy-resistant recalcitrant lesions of inflammatory skin diseases, the clinician is faced with an important unmet need for effective treatment. The involvement of the microvasculature in the pathogenesis of psoriasis and CDLE provides a potential new therapeutic target. So far, a selective therapeutic targeting of microvasculature has not been systematically investigated in these diseases. Vascular laser technology provides a challenging tool to explore this promising option in inflammatory conditions, based on the experience of laser intervention with vascular conditions.

Overall aim:

To explore the value of pulsed dye laser in the treatment of inflammatory skin diseases, inspired by the well established effect in vascular lesions and the evidence of involvement of the microvasculature in inflammatory dermatoses.

Aim 1:

To investigate the efficacy of a vascular laser in spider naevi.

Aim 2:

To explore the potential value of pulsed dye laser in solitary recalcitrant lesions of plaque psoriasis and CDLE.

Aim 3:

To position pulsed dye laser therapy in inflammatory skin diseases based on a systematic literature review.

In the general discussion the value of pulsed dye laser treatment in inflammatory skin diseases will be discussed and treatment recommendations will be provided.

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Vascular lesions 2

2.1 A comparative study of pulsed 532-nm potassium titanyl phosphate laser and electrocoagulation in the treatment of spider nevi

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Dermatol Surg 2010 May;36(5):630-5.

ABSTRACT

Objective: To assess the clinical efficacy and safety of potassium titanyl phosphate (KTP) laser treatment and electrocoagulation (EC) for the treatment of spider nevi (SN).

Method: A randomized single-blind intrapatient comparison study was performed. A blinded observer and patients reported the clinical treatment outcome and pain on a visual analogue scale (0–10). Side effects were noted if present.

Results: Mean physician-rated clinical efficacy scores ± standard error of the mean were 7.7 ± 0.7 for KTP laser and 6.2 ± 0.9 for EC treatment (p =.05). Patient-rated mean clinical efficacy of KTP laser was 8.3 ± 0.6 and of EC was 7.3 ± 0.7 (p =.09). Stratification for potential confounding bias, such as location of SN, central bulging vein, and diameter (p =.25) of the treated SN did not reveal any statistically significant differences between the treatments. Treatment with KTP or EC did not result in scarring or pigmentary changes. Pain was reported for KTP treatment (3.1 ± 0.4) and EC (6.4 ± 0.7) (p <.05).

Conclusion: Clinical efficacy of KTP laser and EC for SN is comparable, although there is a tendency toward an advantage in favor of the KTP laser. KTP laser treatment was less painful.

A comparative study of pulsed 532-nm potassium titanyl phosphate laser and electrocoagulation in the treatment of spider nevi

INTRODUCTION

Spider nevi (SN), also known as spider angiomas, vascular spiders, or naevus araneus, are small conglomerates of dermal capillaries consisting of a central arteriole with radiating thin vessels. The name derives from the central part of a SN, which looks like a spider's body, and the radiating vessels, which resemble multiple spider legs. Redisch and Pelzer classified them based on clinical appearance as one of the four types of telangiectasias.[1] All forms of telangiectasias are thought to occur through the release or activation of vasoactive substances under a multitude of conditions, including anoxia, hormones, chemicals, infections, and physical factors, with resulting capillary or venular neogenesis.[2] SN are benign and may be indicative of underlying systemic disease in extensive cases, although most lesions are unrelated to internal disease.[3,4] Lesions developing during pregnancy or due to oral contraceptives usually resolve spontaneously after delivery or discontinuation of medication. SN are observed in 10% to 15% of healthy adults and young children.[5] Although occurring at any age, two age peaks have been demonstrated: in childhood and early middle age. The face, neck, upper part of the trunk, and arms are the most frequently involved regions.

Whereas the psychological effect of port wine stains is widely recognized, the psychological distress caused by superficial vascular lesions at visible body sites is often underestimated.[6,7] Because the treatment of SN is more a cosmetic than a medical treatment, the treatment modalities should be effective with no side effects such as pigmentary changes and scarring. Traditionally, SN were treated using electrosurgery (electrocoagulation, EC). A needle-like (pin shaped) tip is applied to the central point of the SN (on the so-called feeding vessel) and destroys the feeding vessel using cold point cautery or electrodesiccation.[8] With this procedure, the radiating vessels disappear, avoiding collateral damage to the surrounding skin. Arndt first reported laser therapy for SN in 1982.[9] Thirty-one patients with small vascular lesions were treated with the argon laser, and good to excellent results were observed in patients with SN. The argon laser was the original treatment of choice for vascular lesions, but the continuous nature of the beam produced nonspecific thermal injury in adjacent tissue, increasing the risk of scarring and permanent pigmentary changes. The development of more effective pulsed lasers such as the pulsed dye laser (PDL), pulsed potassium titanyl phosphate (KTP) laser, and pulsed

Table 1A. Patient characteristics: potassium titanyl phosphate–treated spider nevi.

Patient Number	Sex/ Age	Location	Bulging	Diameter (mm)	Clinical Effect (VAS* Score) According to Patient	Clinical Effect (VAS* Score) According to Physician	Pain (VAS Score*)
1	F/49	Face	Yes	9	9.0	7.4	2.4
2	F/62	Face	No	4	2.7	3.8	2.0
3	F/57	Face	No	10	9.2	8.1	1.4
4	F/48	Face	No	3	8.6	9.0	2.8
5	F/46	Face	Yes	5	9.2	8.8	5.7
6	F/66	Face	No	4	8.0	7.1	1.9
7	F/64	Face	No	3	8.1	6.6	2.2
8	F/35	Face	No	6	8.9	9.1	3.1
9	F/65	Face	Yes	4	5.3	3.0	2.7
10	F/37	Face	No	5	10	9.1	5.3
11	F/37	Chest	No	5	10	10	4.0
12	M/26	Face	No	5	10	10	3.6
Mean	49			5.3	8.3	7.7	3.1

* Visual analogue scale (VAS) range 0–10. F, female; M, male.

infrared laser greatly improved the efficacy and decreased the side effects of vascular lasers. Therefore, KTP lasers and PDL lasers are commonly used treatment modalities for SN. In daily practice, EC is easily available and can be instantly performed in outpatient departments. Vascular lasers, on the other hand, are less accessible than EC devices, so the use of lasers for SN is more limited.

To our knowledge, no controlled or comparative studies have been performed to assess the effectiveness of traditional EC with KTP laser treatment. We therefore designed a comparative clinical study to compare the efficacy and safety of both treatments in daily practice.

MATERIAL AND METHODS

Patients

Twelve patients with at least two SN on the face or chest who visited the Department of Dermatology at the Jeroen Bosch Hospital, 's Hertogenbosch, The Netherlands, over a 6-month period were asked to participate in the study. Exclusion criteria were younger than 18 and tanned or Fitzpatrick skin type IV or more. Written informed consent to participate in the study was obtained from all patients.

Table 1B. Patient characteristics: electrocoagulation-treated spider nevi.

Patient Number	Sex/ Age	Location	Bulging	Diameter (mm)	Clinical Effect (VAS* Score) According to Patient	Clinical Effect (VAS* Score) According to Physician	Pain (VAS Score*)
1	F/49	Face	No	4	5.4	2.4	6.7
2	F/62	Face	No	4	2.3	0	3.0
3	F/57	Chest	No	8	9.2	9.1	4.6
4	F/48	Face	Yes	3	8.0	7.8	5.1
5	F/46	Face	Yes	4	8.7	8.2	8.0
6	F/66	Face	No	4	4.0	5.2	5.8
7	F/64	Face	No	4	5.7	3.0	7.6
8	F/35	Chest	No	7	8.7	5.7	7.2
9	F/65	Face	Yes	5	7.8	6.0	2.2
10	F/37	Face	No	5	8.2	8.0	9.1
11	F/37	Chest	No	5	10	10	9.7
12	M/26	Face	No	4	10	9.5	7.3
Mean	49			4.7	7.3	6.2	6.4

* Visual analogue scale (VAS) range 0–10. F, female; M, male.

Study design

At the initial visit, two SN were selected for treatment. If patients had more than two SN, the two most similar in size and appearance were chosen. Randomly, one SN was treated with EC (Hyfrecator, Con Med Corp., Centennial, CO; 2,000 electrosurgical units, position 12) and the other with the KTP laser (VersaPulse VPW, Coherent, Palo Alto, CA), a KTP frequency-doubled neodymium-doped yttrium aluminum garnet (Nd:YAG) laser. A sapphire-chilled contact cooling tip is attached to the handpiece, which cools the epidermal surface before and during the treatment. Treatment parameters were two passes at the feeding vessel with a 4 mm spot size, a fluence of 18 J/cm^2, a frequency of 1.5 Hz, and a pulse duration of 30 ms. The cooling device was set at 3 °C. A water-soluble refractive gel (Aquasonic Clear, Parker Laboratory, Fairfield, NY) was applied before laser treatment was initiated. The maximal diameter of the lesions (mm) was measured. The location of the lesions and the presence of a central bulging vein were reported. All lesions were documented using digital photography before treatment.

After treatment, all patients were instructed to avoid ultraviolet light exposure and to use a sunblock (SPF 50) for the entire follow-up period of 6 weeks. Immediately after treatment, the severity of perceived pain was scored on a visual analogue scale (VAS) ranging from 0 to 10 (0 = no pain, 10 = maximal perceived pain). Adverse events were recorded.

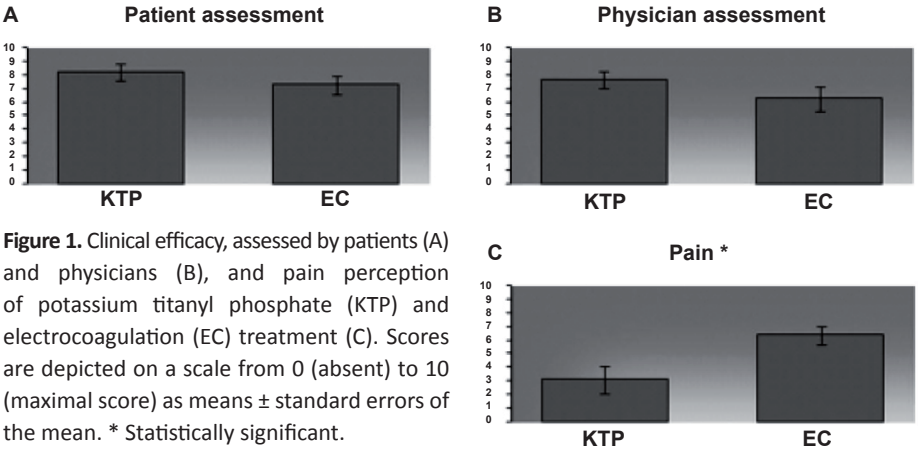

Figure 1. Clinical efficacy, assessed by patients (A) and physicians (B), and pain perception of potassium titanyl phosphate (KTP) and electrocoagulation (EC) treatment (C). Scores are depicted on a scale from 0 (absent) to 10 (maximal score) as means ± standard errors of the mean. * Statistically significant.

Clinical assessments

A blinded independent observer assessed the treatment outcome of all patients at the end of a 6-week follow-up period. The observer did not know which treatment (KTP or EC) had been given. SN were compared to baseline photography on a VAS ranging from 0 (no improvement at all) to 10 (total disappearance of the SN). The patients performed the same assessment using an identical VAS. Side effects were noted if present (e.g., hypopigmentation, hyperpigmentation, and scar formation).

Statistical analysis

Two-tailed paired *t*-tests were performed using Statistica statistical software version 6.0 (Statsoft, Tulsa, OK) to compare the difference between pre- and post-treatment VAS scores. A statistical significant difference was apparent if $p < .05$.

RESULTS

Patient characteristics

Twelve patients (1 male, 11 female) with mean age ± standard error of the mean of 49.3 ± 3.9 were included. Patient characteristics are depicted in tables 1A and 1B.

KTP versus EC: patient assessments

Patients rated the clinical efficacy of KTP and EC treatment of their SN on a VAS of 0 to 10. The mean patient assessment of KTP treatment was 8.3 ± 0.6, whereas the mean score was 7.3 ± 0.7 for treatment of SN with EC. This difference was not statistically significant but showed a tendency toward significance in favor of the KTP-treated SN ($p = .09$) (figure 1A).

KTP versus EC: physician assessment

The mean physician VAS scores were 7.7 ± 0.7 for KTP and 6.2 ± 0.9 for EC. Similar to the patient derived scores, this difference was borderline statistically significant in favor of treatment of SN with KTP (p =.05) (figure 1B).

Confounders: location, bulging, and diameter of SN

Stratification for potential confounding bias, such as location of SN, central bulging vein, and diameter of the treated SN did not reveal any significant results. Patients had at least two SN, 20 (83%) were located in the face and 4 (17%) on the chest (p >.05). Six SN had a central bulging vein; three of those were treated with KTP and three with EC (p >.05). Diameters of the lesions before treatment were comparable: 5.3 ± 0.6 for the KTP-treated SN and 4.7 ± 0.4mm for the EC-treated SN (p =.25). The three mentioned variables did not correlate to the degree of response to treatment with KTP or EC (all p >.05; data not shown).

Side effects of treatments

Treatment with KTP or EC did not result in hypopigmentation, hyperpigmentation, or scar formation in the investigated cases. Pain was reported as the only adverse event (mean: KTP, 3.1 ± 0.4; EC, 6.4 ± 0.7). This result was statistically significant in favor of KTP laser treatment (figure 1C).

DISCUSSION

Because EC and KTP laser treatment are both commonly used methods to treat SN, a randomized single-blind intrapatient comparative study was performed in which the efficacy and safety of these treatments were assessed.

The data from the present study demonstrate that EC and KTP laser therapy are both safe and effective treatment options for SN. Although no statistically significant difference was observed, there was a tendency toward significance with respect to the clinical outcomes in favor of the KTP laser–treated SN. Patients mentioned significantly less pain after the laser treatment than after EC.

The fact that the vascular laser targeted the feeding vessel and the radiating vessels, whereas the electrocoagulation tip targeted only the feeding vessel, may explain the clinical results.

The smaller amount of tissue damage caused by laser treatment and the presence of a water-cooled sapphire laser chill tip, causing some local anesthesia, may explain the difference in painfulness between the treatments. Side effects such as hypopigmentation, hyperpigmentation, and scar formation were not observed in our patients, which makes both EC and KTP suitable treatment options.

Figure 2. Clinical photographs of spider nevi before (A) and after (B) potassium titanyl phosphate (KTP) treatment together with before (C) and after (D) electrocoagulation (EC) treatment. Photographs before (E) and after (F) KTP (19.1.1 & 19.2.1) and EC (19.1.2 & 19.2.2) in the same patient.

In the last decade, pulsed lasers have become more commonly used for the treatment of SN.[10] Tan and Vinciullo reported a retrospective study with a total clearance rate of 93% of SN after a single PDL treatment.[11] The efficacy of the KTP laser in the treatment of SN was first described in 24 patients, of whom 20 (83%) showed disappearance or moderate improvement after one treatment session.[12] These results indicate that a PDL would be the laser of choice for SN and other telangiectasias, but in a left–right intrapatient treatment of PDL and KTP for facial telangiectasias, the 532-nm KTP laser was found to be more effective than the PDL for individual telangiectasias and

telangiectatic erythema after each treatment.[13] The KTP laser has been shown to be effective in the treatment of a variety of vascular lesions; the major disadvantage is the limited depth of skin penetration due to its short wavelength. One might hypothesize that if this study were performed with vascular lasers with a greater penetration depth, like the long-pulsed PDL or the long-pulsed Nd:YAG laser, even better results might have been achieved in favor of the laser, but PDL laser treatment may eventually result in the formation of purpura, which may result in longer downtime for the patient.

The benefits of various laser systems are well known, but the main point of this study is that treatment of SN with EC is effective, well tolerated, and more or less comparable with treatment with a KTP laser (figure 2). Hence, the physician who possesses only a hyfrecator is not undertreating his patients with SN, although treatment with KTP laser proved to be less painful.

In conclusion, the clinical efficacy of KTP laser and EC treatment for SN is comparable, although there is a tendency toward an advantage in favor of the KTP laser. KTP laser treatment was found to be less painful. Therefore, if a KTP laser is available, this might be the best choice for treatment of SN, although if a laser is not available, EC has proven to be a solid alternative.

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Inflammatory diseases 3

3.1 Efficacy of the pulsed dye laser in the treatment of localized recalcitrant plaque psoriasis: a comparative study

Erceg A, Bovenschen HJ, van de Kerkhof PC, Seyger MM

Br J Dermatol 2006 Jul;155(1):110-4.

3.2 Pulsed dye laser versus treatment with calcipotriol/betamethasone dipropionate for localized refractory plaque psoriasis: effects on T-cell infiltration, epidermal proliferation and keratinization

Bovenschen HJ, Erceg A, van Vlijmen-Willems I, van de Kerkhof PC, Seyger MM

J Dermatolog Treat 2007;18(1):32-9.

3.3 Validation of clinical and image skin scoring systems for a single chronic discoid lupus erythematosus lesion

Erceg A, de Jong EM, van Lingen RG, De Boo TM, van de Kerkhof PC, Seyger MM

J Dermatolog Treat 2009;20(1):32-5.

3.4 Efficacy and safety of pulsed dye laser treatment for cutaneous discoid lupus erythematosus

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J Am Acad Dermatol 2009 Apr;60(4):626-32.

ABSTRACT

Background: Localized chronic plaque psoriasis, resistant to local therapy, may be very hard to treat. The treatment of these lesions with a pulsed dye laser (PDL) has been described before, but a comparative study between the PDL and a potent topical treatment has never been performed.

Objectives: To compare the efficacy of the PDL in the treatment of localized, recalcitrant plaque psoriasis with a potent topical therapy, using calcipotriol/betamethasone dipropionate (Dovobet®) as an active comparator.

Methods: Eight patients with psoriasis were treated with both PDL (585 nm) and calcipotriol/betamethasone dipropionate in an open, intrapatient, left–right comparison. A plaque severity score (sum score) and photographs were used to document the course of therapy. Patients reported pain on a visual analogue scale.

Results: Both treatments were well tolerated, although one patient left the study due to post-PDL treatment pain. A significant difference in the sum score 12 weeks after treatment was seen in favour of the PDL (62% vs. 19% reduction; $p < 0.05$). Scores for erythema declined significantly at week 12 in both the PDL and the calcipotriol/betamethasone dipropionate group ($p < 0.001$). Induration and desquamation scores were significantly reduced at week 12 in the PDL group, without a statistically significant reduction in calcipotriol/betamethasonetreated lesions. The pain scores declined with progressive PDL treatments, although not statistically significantly.

Conclusions: PDL treatment might be considered for the treatment of localized, recalcitrant plaque psoriasis, when other topical therapies have failed.

Efficacy of the pulsed dye laser in the treatment of localized recalcitrant plaque psoriasis: a comparative study

INTRODUCTION

So far, no consensus exists on the position of the pulsed dye laser (PDL) in the treatment of psoriasis. Multiple previous studies have shown different results, ranging from complete remission to no improvement at all.[1–7] It is difficult to compare the results of these studies, because they all used different treatment modalities. The number of treatments varied from only one treatment up to five. There was also a wide variation in laser parameters such as spot size (diameter 5–7 mm), energy fluence (2–9 J/cm^2) and pulse duration (0.2–1.5 ms). There are no studies comparing PDL treatment with other well-known treatments for psoriasis.

In plaque psoriasis, the first comparative study was done by Zelickson *et al*.[4] They compared two different pulse durations of PDL treatment with each other, using fluences varying between 7.5 and 8.5 J/cm^2, and with triamcinolone acetonide 0.1% ointment twice daily for 10 weeks. Using global scores, they found a statistically significant clinical improvement of the PDL-treated site, compared with the triamcinolone-treated site. Bjerring *et al*. compared the PDL (0.2 ms, 2–7 J/cm^2) with dermabrasion.[6] Dermabrasion gave complete remission in five of six patients, whereas such improvement was reached in only three of 11 patients treated with PDL.

Neither dermabrasion nor triamcinolone acetonide 0.1% ointment, however, are standard treatments for psoriasis. The latter is regarded as a relatively mild corticosteroid for the treatment of psoriasis. There are no comparative studies between PDL and first-line topical treatments of psoriasis. Because PDL treatment is time consuming, expensive and painful, it is not a first-choice treatment for psoriasis. In chronic, localized, therapy-resistant plaque psoriasis, however, PDL treatment might provide an adequate solution.[8,9]

In order to examine the position of the PDL in the treatment of localized recalcitrant plaque psoriasis, we compared its clinical efficacy and tolerability with an active comparator: calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g ointment (CB) (Daivobet®/Dovobet®; Leo Pharma, Ballerup, Denmark). This two-compound product is a highly effective treatment for psoriasis. Clinical studies have demonstrated that up to 4 weeks of treatment with CB once daily gives superior efficacy and similar or better tolerability than once or twice daily application of its individual components.[10–13]

In a left–right comparison, patients with recalcitrant psoriasis were treated with both CB and the PDL. CB treatment was given for a period of 4 weeks. The number of PDL treatments varied between one and three, with a 2-week interval between treatments.

MATERIALS AND METHODS

Patients

Eight patients aged at least 18 years with stable, symmetrical, recalcitrant plaque psoriasis were included in the study. Recalcitrant psoriasis was defined as: "not responding to any topical therapy (ointments and creams), including ultrapotent corticosteroids and vitamin D3 derivatives and combination products or combination therapy with more than one topical treatment". Patients were excluded if they had received systemic antipsoriatic agents within 8 weeks prior to the study, or phototherapy [psoralen plus ultraviolet (UV) A or UVB] within 4 weeks prior to the start of the study. Patients had used no topical treatment for at least 2 weeks. Other exclusion criteria were pregnancy, lactation and a history of photosensitivity. This study was approved by the medical ethics committee. Written informed consent was obtained from all patients.

Study design

Two weeks before the start of treatment, 10% salicylic acid in white vaseline was prescribed for 2 weeks in order to standardize and optimize the pretreatment situation for both topical treatment and laser treatment. It is particularly necessary to minimize scaling before PDL treatment. At the initial visit, two similar, contralateral psoriatic lesions of at least 12 cm^2 were selected. These plaques were similar in terms of body localization and clinical severity score. One of the plaques was treated with CB once daily, for a period of 4 weeks. The contralateral lesion was treated with the PDL (Photogenica V laser; Cynosure, Chelmsfort, CA, U.S.A.) at the initial visit and after 2 and 4 weeks. A pulse duration of 0.45 ms with a wavelength of 585 nm was constantly used. Comparing all previous studies with different fluences, spot sizes and time intervals between two treatments, the best results were achieved with a fluence of 8.5 J/cm^2, a spot size with a diameter of 5 mm and a treatment interval of 2 weeks. In order to compare these findings with our own experience, a psoriatic plaque of a patient not included in our study was treated with four different fluences: 5.5, 6.5, 7.5 and 8.5 J/cm^2. One month after PDL treatment, pictures were taken of the treated area and complete clearance was noticed at the site treated with 8.5 J/cm^2 (figure 1). We therefore used an energy fluence of 8.5 J/cm^2 and a spot size of 5 mm in all patients and during all

Figure 1. Clinical photograph of a psoriatic plaque treated with 5.5, 6.5, 7.5 and 8.5 J/cm^2 in four quadrants, when determining the fluence used in the present study (8.5 J/cm^2).

three treatments. The area treated with laser had an overlap of 10–20% per shot. Prior to the PDL treatment, arachis oil was applied on the psoriatic plaques, in order to reduce the amount of scattering. Local anaesthesia was given during and shortly after the laser treatment, using a cooling device (Cryo 5 cooling device; Zimmer Elektromedizin, Neu-Ulm, Germany).

After the 4 weeks of treatment with both PDL and CB, patients entered the follow-up period of 8 weeks. If the PDL-treated plaque showed residual crusting at the planned second and third visits, PDL treatment was postponed for 1 week, until the crusting had resolved, for safety and to optimize efficacy. Clinical efficacy was scored at baseline, and after 4 and 12 weeks. Adverse events were recorded and patients reported pain on a visual analogue scale (VAS).

Clinical assessments

At every visit photographs of the two target plaques were taken and sum scores were assessed. The sum score is a cumulative measure which includes scores for erythema, induration (plaque thickness) and scaling on the following scale: 0, absent; 1, minimal (very light pink, hardly any elevation, rare scale); 2, mild (light red/pink, slight elevation, poorly defined scale); 3, moderate (red, moderate elevation, defined scales); 4, severe (very red, marked ridge, heavy scaling). Finally, a global sum score (range 0–12) was defined as the sum of all three scores together, reflecting plaque severity.

Table 1. Number of pulsed dye laser (PDL) sessions, time span between these sessions, efficacy and drop-out.

Patient	Number of PDL sessions	Residual crusting	Postponed 1 week	Remarks
1	3	No	No	Excellent response; hyperpigmentation
2	3	No	No	Excellent response; hyperpigmentation
3	3	No	No	-
4	1	No	No	Dropped out due to pain, data not analysed
5	3	Yes	Yes	PDL treatment at weeks 0, 3 and 6; excellent response; hyperpigmentation
6	1	Yes	No	Excellent response; hyperpigmentation
7	3	No	No	-
8	3	Yes	Yes	PDL treatment at weeks 0, 3 and 6

VAS scores (range 0–10) were used to measure the level of pain during treatment. A score of 0 represented a total absence of pain and 10 represented maximum pain. Patients reported these scores after PDL treatment.

Statistical analysis

All analyses were carried out using Statistica® statistical software, version 6.0 (StatSoft, Tulsa, OK, U.S.A.). To compare sum scores between different moments in time during treatments, we performed two-way analyses of variance. If significant, Duncan's post hoc comparison was performed. $p < 0.05$ denoted the presence of a statistically significant difference.

RESULTS

Patient population

Eight Caucasian patients, four men and four women, with localized recalcitrant moderate-to-severe symmetrical plaque psoriasis, participated in this investigation. Their mean ± SEM age was 52 ± 10 years, and the mean ± SEM duration of psoriasis was 21 ± 8 years. One patient terminated the trial early due to an adverse event after the first PDL treatment. This patient considered the treatment too painful. Data of this patient were not analysed. A further patient required only one PDL session to achieve an excellent response. Two patients had PDL sessions at weeks 0, 3 and 6 instead of 0, 2 and 4, because of residual crusting (table 1).

Sum scores during therapy

At baseline, sum scores (mean ± SEM) were 7.6 ± 0.3 in the PDL group and 7.4 ± 0.3

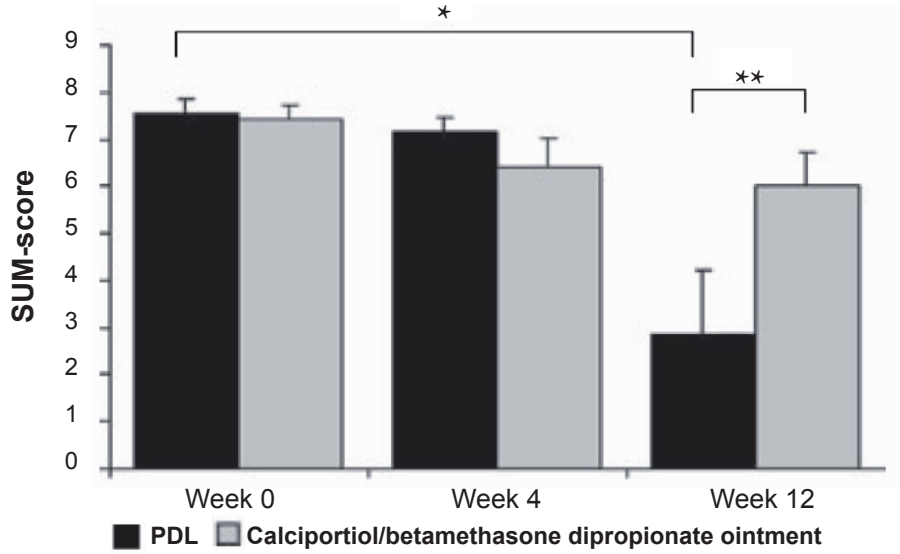

Figure 2. Sum scores (0–12) during pulsed dye laser (PDL) treatment, compared with topical calcipotriol/betamethasone dipropionate ointment therapy (mean ± SEM). Statistical significance: *p = 0.001; **p = 0.04.

in the CB group. Four weeks after the start of treatment no statistically significant change had been observed, although a tendency to lower sum scores was seen in both groups. Twelve weeks after treatment, however, the sum score declined to 2.9 ± 1.4 in the PDL group (p =0.001), whereas in the CB group the sum score dropped only to 6.0 ± 0.7 (p =0.10). Figure 2 illustrates these results.

Differences in sum score (mean ± SEM) between the PDL and CB groups were 0.2 ± 0.1, 0.7 ± 0.8 and 3.1 ± 1.6, at weeks 0, 4 and 12, respectively, and in favour of PDL at week 12. The sum score difference at week 12 was statistically significant compared with week 0 (p = 0.04) and week 4 (p =0.02). These results are depicted in figure 2.

Erythema, induration and desquamation

Four weeks after the start of treatment no statistically significant result was observed for separate erythema, induration and desquamation scores, although a tendency towards lower scores was observed.

Scores for erythema declined statistically significantly at week 12 in both the PDL (3.3 ± 0.2 at week 0 to 1.1 ± 0.6 at week 12; $p < 0.001$) and the CB groups (3.1 ± 0.1 at week 0 to 2.4 ± 0.2 at week 12; $p < 0.01$). Induration and desquamation scores were significantly reduced at week 12 in the PDL group, but not in the CB group (figure 3).

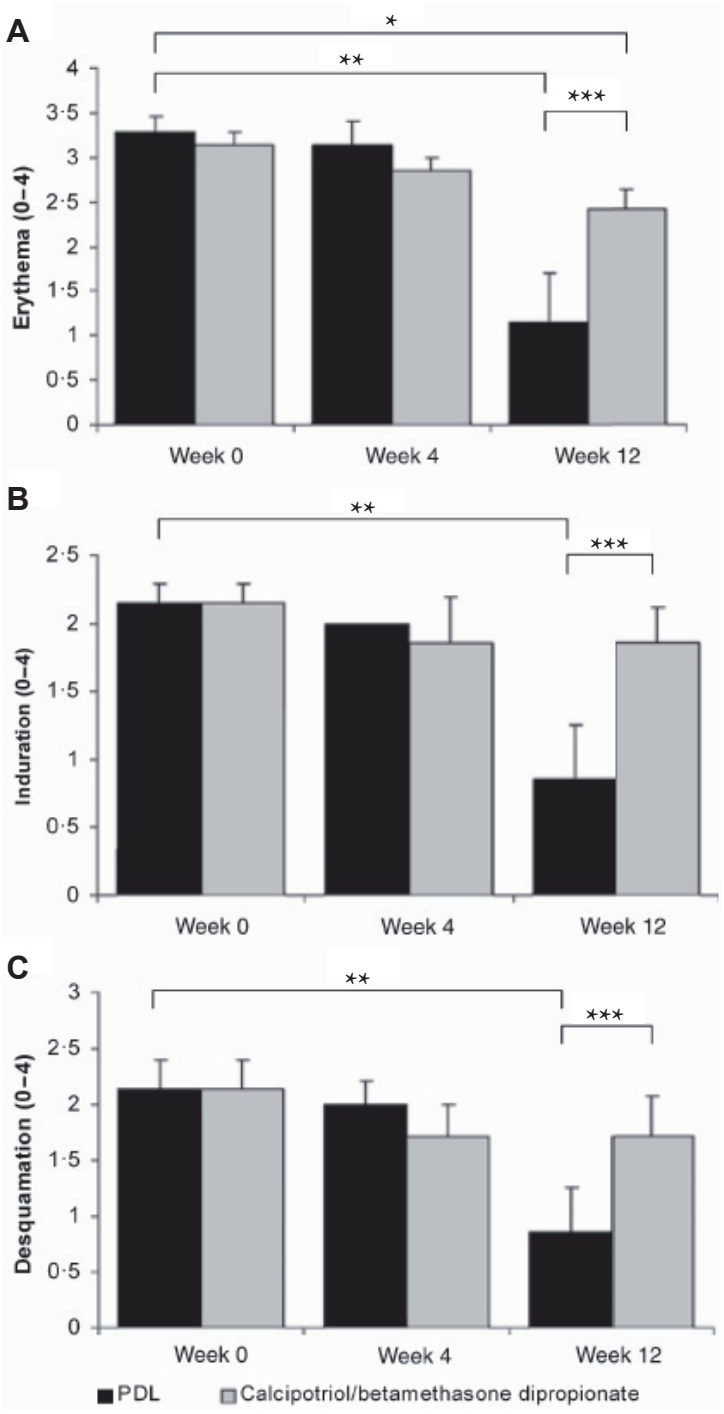

Figure 3. Separate clinical scores (0–4) for the individual components: erythema (A), induration (B) and desquamation (C) (mean ± SEM).
Statistical significance: *$p < 0.01$; **$p < 0.001$; ***$p < 0.05$.

Side-effects

Patients reported pain at the treated site as the major side-effect of PDL therapy. The overall pain score (mean ± SEM) on a 0–10 VAS was 6.5 ± 0.4. No correlation was found between pain score and treatment success. Interestingly, pain scores declined from 7.0 ± 0.6 after the first, to 6.7 ± 0.9 and 5.7 ± 0.8 after the second and third PDL sessions, respectively ($p > 0.05$). Four patients developed residual hyperpigmentation after the PDL treatment.

Long-term follow-up

After more than 6 months of follow-up, the four patients with a complete response to PDL still had clearance of the treated plaque. Hyperpigmentation was still visible. However, three of these four patients had needed systemic treatment for an exacerbation of their psoriasis, and therefore the follow-up observation on the PDL-treated plaque was no longer reliable.

DISCUSSION

In the present study patients were treated for 4 weeks with the PDL and CB in an open, intrapatient, left–right comparison. After 4 weeks of treatment, no statistically significant result was observed in either treatment. The majority of patients (five out of seven) received their third and last PDL treatment only at week 4; it is thus likely that at week 4 the clinical results of the PDL treatment were not yet apparent. The results after 4 weeks of CB treatment, however, were unexpected. Although a tendency to a decline in sum score was observed, there was no statistically significant improvement of the psoriatic lesions. This is in contrast with earlier studies, in which CB showed good results after 4 weeks of treatment.[10–13] The explanation for this may be that we selected patients with plaque psoriasis that had previously been resistant to potent topical treatments. Secondly, it is possible that patients' compliance may not have been optimal. Although all patients claimed to have applied the ointment once daily, we did not check the residual ointment after the 4 weeks of topical treatment.

In contrast, after 8 weeks of follow-up, at week 12, the sum score had significantly declined further in the PDL group. We also observed a reduction in the CB-treated group, but this decline was not significant. Remarkably, in both groups the score for erythema declined significantly after 12 weeks, whereas induration and desquamation scores declined significantly only in the PDL group.

Four of seven patients reached complete clearance of the psoriatic lesions 8 weeks after the final laser treatment. In these patients, all of whom had skin type I, II or III, there was some degree of hyperpigmentation visible at the treated

area. Mild hyperpigmentation was also present in the patients treated with PDL in previous studies.[2–4] Although some studies mentioned other side-effects such as hypopigmentation and atrophic scarring, we did not see these effects in our patients.[3,4] Patients who had complete remission of the PDL-treated plaque had a prolonged remission: after approximately 6 months of extra follow-up there were still no signs of relapse.

There was a tendency towards a decline in the reported pain scores after successive laser treatments, although this was not significant. Pain has also been mentioned in previous studies as a disadvantage of the PDL treatment. By providing local anaesthesia with a cooling device during and shortly after the laser procedure, our patients considered the laser treatment to be reasonably tolerable.

Studies on the efficacy of treating chronic psoriatic plaques with the PDL, compared with a first-line topical therapy for psoriasis, have not previously been performed. Although we noticed a significant improvement in the laser-treated areas at week 12, compared with those treated with the active comparator, the utility of the PDL as a standard therapy for psoriasis is limited. Due to the small spot size and the post-treatment pain, laser treatment has to be restricted to only circumscribed and therapy-resistant psoriatic plaques.

Limitations of the present study include the lack of blinding, the small patient group and the possible poor compliance to topical treatment. Moreover, sum scores might have been influenced by the pretreatment with 10% salicylic acid, which is necessary for PDL treatment on severely scaling plaques. However, pretreatment might also have enhanced the penetration of CB.

In conclusion, PDL treatment might be considered for the treatment of localized, recalcitrant plaque psoriasis, when topical therapies have failed or are contraindicated. The treatment is well tolerated although pain and hyperpigmentation can be experienced. These side-effects were acceptable in most patients.

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ABSTRACT

Background: Selective photothermolysis of diseased capillaries by pulsed dye laser (PDL) treatment has been described as a mechanism for long-lasting clearance of psoriatic plaques.

Aim: To evaluate PDL and a two-compound formulation of calcipotriol/betamethasone dipropionate ointment for the treatment of localized, recalcitrant plaque psoriasis.

Methods: Eight psoriatic patients were treated for 4 weeks with both PDL and topical calcipotriol/betamethasone dipropionate in an open, intra-patient, left-right comparison. Biopsies were analyzed for T-cell subsets, cells expressing NK-receptors, epidermal proliferation, differentiation and epidermal thickness.

Results: After active treatment, both treatments showed statistically significant, but comparable improvements of T-cell subsets, epidermal proliferation, differentiation and epidermal thickness. In line with the clinical results, after an 8-week follow-up period statistically significant further reductions were observed for dermal CD3+, CD4+, CD45RO+, CD2+ T cells, epidermal CD3+, CD8+, CD45RO+, CD2+, CD25+ T cells and the epidermal parameters for the PDL-treated plaques, in contrast to the topically treated plaques.

Conclusion: After 8 weeks of follow-up, PDL treatment for localized and recalcitrant plaque psoriasis resulted in persistent reductions of activated and memory effector T-helper cells in the dermis, cytotoxic T cells in the epidermis, and normalization of epidermal proliferation and keratinization, in contrast to treatment with calcipotriol/betamethasone dipropionate ointment.

Pulsed dye laser versus treatment with calcipotriol/ betamethasone dipropionate for localized refractory plaque psoriasis: effects on T-cell infiltration, epidermal proliferation and keratinization

INTRODUCTION

Pulsed dye laser (PDL) treatment for vascular disorders of the skin has been an accepted treatment modality since the early 1980s.[1] The PDL-specific 585 nm wavelength of laser light is preferentially absorbed by the oxyhemoglobin present in small vessels in the dermis, where the heat leads to coagulation of and ablation of blood vessels (selective photothermolysis).[1,2] A histological hallmark of psoriasis is dilatation and tortuosity of the capillary bed in the dermis, which has been reported to be an early phenomenon in the pathogenesis of psoriatic plaques.[3-5] When these diseased capillaries are eliminated by PDL treatment, the severity of psoriatic plaques is likely to improve.[6,7]

Immunohistochemical assessments of the effect of PDL treatment on severe recalcitrant psoriasis have sparsely been reported.[8,9] Clinical efficacy of PDL treatment for psoriasis is still controversial. Some reports indicate no improvements at all, whereas others report long-lasting clearance of plaques.[8-14] Only three clinical comparative studies have been performed so far. PDL treatment showed higher clinical efficacy compared with topical triamcinolone acetonide 0.1% treatment in a study by Zelickson *et al*., whilst dermabrasion had better clinical results than treatment with PDL in a study by Bjerring *et al*.[9,14] Erceg *et al*. gave a detailed report of the clinical results of the present study. In that report, PDL showed an outstanding efficacy as compared to calcipotriol/betamethasone dipropionate ointment. It was concluded that PDL treatment might be considered for the treatment of localized, therapy-resistant plaque psoriasis, when other topical therapies have failed.[15]

Two studies have examined psoriatic skin biopsies during and after PDL treatment. First, Zelickson *et al*. observed clinical and histological improvement using hematoxylin and eosin (HE) stainings and confocal laser microscopy. Various histopathological features improved, including the diseased dermal vasculature.[9] Furthermore, Hern *et al*. assessed markers for angiogenesis, lymphocyte infiltration (CD4 and CD8), epidermal thickness and keratinocyte proliferation, before and 2 weeks after three PDL exposures to treat psoriasis. Vascular improvements were found to be limited to the papillary dermis, whereas no changes in the upper reticular dermis were observed. Adhesion molecules did not change during treatment. The CD4+ and CD8+ T-cell infiltrate exclusively reduced in the superficial dermis, but not in the epidermis

or in the reticular dermis. Epidermal thickness improved, whereas keratinocyte proliferation was not significantly altered after treatment. Hern *et al*. hypothesized that dermal capillary changes alone are not likely to be causal in psoriasis, but might be important in the facilitation of traffic of pathogenic T cells into the skin and in perpetuation of the psoriatic process.[8] Vissers *et al*. showed an immunohistochemical analysis of the effect of treatment with calcipotriol, once daily, and betamethasone, once daily, on psoriatic plaques.[18] Yet, there are no studies available that examined the dynamics of T-cell subsets during treatment with the two-compound formulation, which contains both calcipotriol and betamethasone dipropionate.

To study the dynamics of activated (CD2, CD25) and memory effector (CD45RO) T cells of the T-helper (CD4) and cytotoxic (CD8) subset and epidermal markers for proliferation (Ki67) and differentiation (K10) during PDL treatment, we performed an intra-patient left/right comparison: one plaque treated with PDL and the contralateral plaque with a well-established two-compound topical treatment, calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g ointment, once daily.[17,18]

METHODS

Patients

Eight patients of at least 18 years old with stable, symmetrical, recalcitrant plaque psoriasis were included in the present study. Recalcitrant psoriasis was defined as "not responding to any topical therapy (ointments and creams), including ultra potent corticosteroids and vitamin D_3 derivatives and combination products or combination therapy with more than one topical treatment". Patients were not treated with systemic anti-psoriatic medication (stopped ≥ 8 weeks prior to the study), phototherapy (discontinued ≥ 4 weeks prior to the study start), or topical treatment (stopped at least 2 weeks prior to the baseline visit). Other exclusion criteria were pregnancy, lactation and a history of photosensitivity. The medical ethics committee approved the present study and written informed consent was obtained from all patients.

Study design

Two weeks before the start of treatment, 10% salicylic acid in white vaseline was prescribed for two weeks in order to standardize and optimize the pretreatment situation for both topical treatment and laser treatment. For PDL treatment especially it is essential to minimize scaling. At the initial visit, two similar, contralateral psoriatic lesions of at least 12 cm^2 were selected. These plaques were controlled, in terms of body localization and clinical severity score. One of the plaques was treated with calcipotriol/betamethasone dipropionate ointment (Daivobet®/Dovobet®; LEO

Table 1. Used monoclonal antibodies for immunohistochemistry.

Antibody	Concentration	Specificity	Marker for	Source
MIB-1	1:200	Ki67	Keratinocyte proliferation	DAKO, Copenhagen, Denmark
RKSE60	1:100	Keratin 10	Normal keratinization	Monosan Laboratories, Uden, The Netherlands
UCHT1	1:100	CD3	Pan T cells	DAKO, Copenhagen, Denmark
MT310	1:200	CD4	Helper T cells	DAKO, Copenhagen, Denmark
DK25	1:200	CD8	Cytotoxic T cells	DAKO, Copenhagen, Denmark
UCHL1	1:100	CD45RO	Memory effector T cells	DAKO, Copenhagen, Denmark
4KB5	1:200	CD45RA	Naive T cells	DAKO, Copenhagen, Denmark
MT910	1:200	CD2	Pan T cells, but upregulated on activated T cells	DAKO, Copenhagen, Denmark
ACT-1	1:200	CD25	Il-2 receptor, early activation marker	DAKO, Copenhagen, Denmark
HP-3D9	1:100	CD94	NK cells and some T cells	DAKO, Copenhagen, Denmark
191B8	1:100	CD161	NK-T cells	Immunotech, Marseille, France
110416	1:100	GITR/ TNFRSF18	Glucocorticoid-induced tumor necrosis factor receptor, inhibitory receptor of regulatory T cells, some macrophages	R&D Systems, Minneapolis, USA

Pharma, Ballerup, Denmark), once daily, for a period of 4 weeks. The contralateral lesion was treated with the PDL (Photogenica V laser; Cynosure, Chelmsfort, CA, USA) at the initial visit, and after 2 and 4 weeks. An energy fluence of 8.5 J/cm^2, a pulse duration of 0.45 ms with a wavelength of 585 nm, a spot size of 5 mm with an overlap of 10-20 % per shot was constantly used in all patients and during all treatments. Local anesthesia was given during and shortly after the laser treatment, using a cooling device (Cryo 5 cooling device; Zimmer Elektromedizin).

After the 4 weeks of treatment with both PDL and calcipotriol/betamethasone dipropionate ointment patients entered the follow-up period of 8 weeks. If the PDL-treated plaque showed residual crusting at the planned second and third visit, PDL-treatment was postponed for one week, until the crusting had resolved, in order to secure safety and to optimize efficacy. Clinical efficacy was assessed and biopsies were taken at baseline, and after 2, 4 and 12 weeks.

Clinical assessment

At baseline and at weeks 2, 4 and 12, clinical severity assessments of the treated plaques were performed. SUM-scores (0-12) were obtained by one single observer during the whole study period. SUM-scores represent the cumulative score for erythema (0-4), induration (0-4) and desquamation (0-4). A SUM-score of 0 represents “no psoriasis” and a SUM-score of 12 reflects the ‘worst imaginable clinical severity of the psoriatic plaque’.

Biopsies

All biopsies (4 mm) were taken at a central, representative site in the target lesions. At

baseline, two biopsies were taken: one of distant uninvolved skin and one of lesional psoriatic skin. At weeks 2, 4 and 12, two biopsies were taken, only of both treated plaques. The distant uninvolved skin served as a control to compare the after-treatment situation with the baseline values. Before the biopsy procedure, local anaesthesia was given (xylocaine/adrenaline 1:100.000). Skin defects were closed with one suture. The samples were embedded in Tissue Tek OCT compound (Miles Scientific, Naperville, IL, USA), instantly frozen in liquid nitrogen and stored at -80 °C until use.

Immunohistochemical staining

Sections were sliced 7 µm thick and were air-dried for 30 minutes. Then the sections were fixed in cold acetone for 10 minutes. After blocking 5 minutes for endogenous peroxidase, using 0.2% sodium azide, they were washed in PBS for 10 minutes. Subsequently, sections were incubated with the primary antibodies for 1 hour. The monoclonal antibodies used are listed in table 1. Sections were washed in PBS for 15 minutes. The secondary IgG labeled polymer HRP anti-mouse EnVision+ (DAKO, Copenhagen, Denmark) was added for 30 minutes. The sections were washed again for 15 minutes in PBS. To visualize the staining we used AEC+ high sensitivity substrate chromogen for 10 minutes (DAKO). Counterstaining was performed with Mayer's hematoxylin (Sigma, St Louis, MO, USA). The sections were washed in tap water, dried and mounted in glycerol gelatin (Sigma).

HE staining

Furthermore, from each patient we performed hematoxylin and eosin (HE) stainings. After dehydration in alcohol and histosafe, these sections were mounted in Permount. With these HE sections, it was verified that the baseline biopsies fulfilled the psoriasis-specific histological criteria.

Manual quantification

Quantification of T-cell subsets was performed with light microscopy at 200X magnification. In all sections CD3, CD4, CD8, CD45RO, CD45RA, CD2, CD25, GITR, CD94 and CD161 positive cells in the epidermis were counted from the basement membrane up to the stratum corneum across the whole section (4 mm). Cells in the dermis were counted from the basement membrane down to 100 µm under the basement membrane and also across the whole section. Quantitative cell counts were expressed in "positive cells per mm skin length".

Digital image analysis

In order to analyze Ki67 positive cells, three representative digital photographs were made at 100x magnification. Each photograph was analyzed using IP-lab software. A line, with known length and following the stratum basale, was drawn

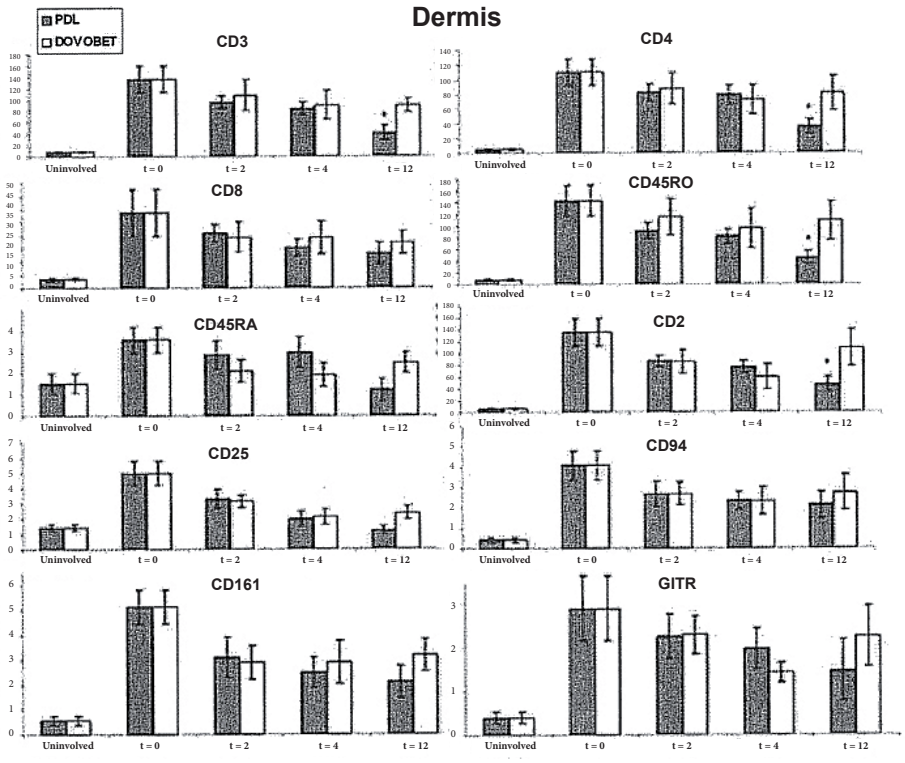

Figure 1. Dermal counts for T-cell subpopulations and cells expressing NK-receptors during treatment with PDL and calcipotriol/betamethasone dipropionate ointment, at baseline, after 2 and 4 weeks of treatment, and after an 8-week follow-up period.

after choosing a representative "region of interest" (ROI). All positive cells above this line were counted and expressed in the unit "positive cells per mm length of basement membrane". For quantification of keratin 10 (K10) positive cells, digital photographs were made at 50x magnification. Using IP-lab software a ROI was set for the analysis of K10, in a representative area of the particular section. The ROI was chosen in only the epidermal compartment and possible dermal tissue in the ROI was subtracted. The total area of the epidermal compartment in the ROI and the K10+ area were measured using IP-lab software. Epidermal differentiation was defined as: the percentage K10+ epidermal surface area. Epidermal thickness was measured in HE sections with the help of IP-lab software, by calculating the means of the three smallest and three largest vertical lengths of the epidermis, without the stratum corneum. The mean value per section was determined "epidermal thickness".

Statistical analysis

All analyses were carried out using Statistica® statistical software, version 6.0. Two-

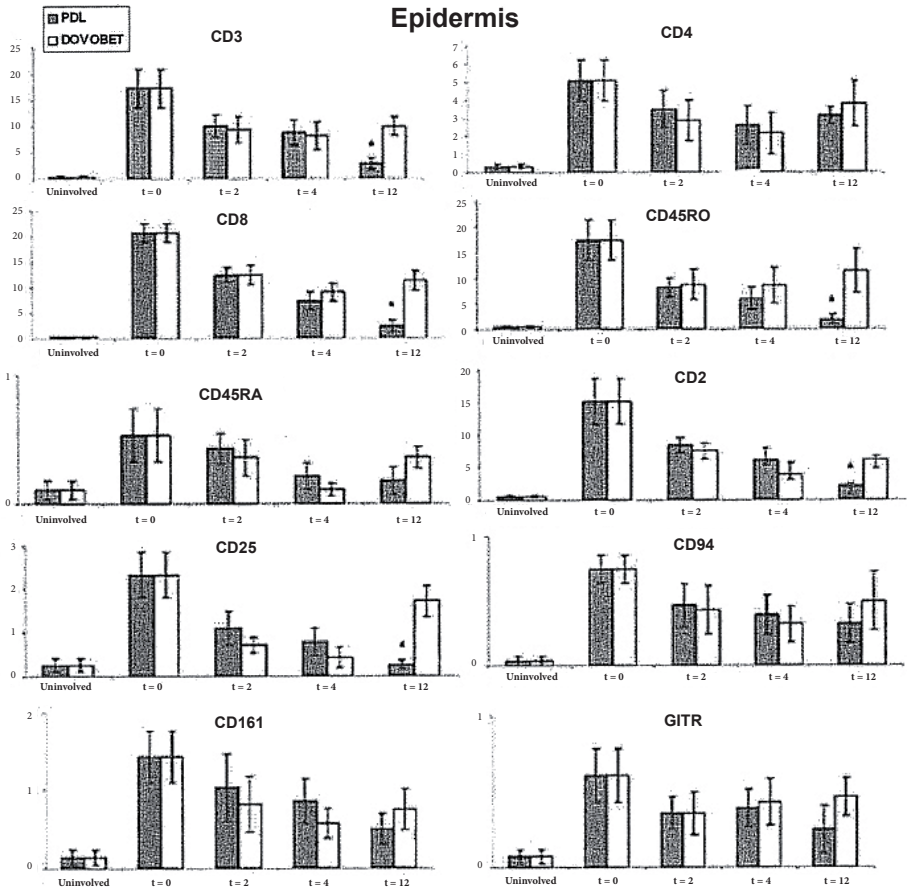

Figure 2. Epidermal counts for T-cell subpopulations and cells expressing NK-receptors during treatment with PDL and calcipotriol/betamethasone dipropionate ointment, at baseline, after 2 and 4 weeks of treatment, and after an 8-week follow-up period.

way analyses of variance (ANOVA) were performed. If significant, Duncan's post-hoc comparison was performed. A *p*-value of less than 0.05 denoted the presence of a statistical significant difference.

RESULTS

Patient population

A total of eight patients with recalcitrant and symmetrical plaque psoriasis participated; four were male and four were female. One patient early dropped out due to an adverse event (pain) at the PDL-treated plaque. The histology (HE) of

all baseline biopsies of the seven evaluable patients fulfilled the psoriasis-specific criteria. Two patients had PDL sessions at week 0, 3 and 6 instead of 0, 2 and 4, because of residual crusting.

Clinical assessment

After 12 weeks, the mean SUM-score reduced 62% in the PDL-treated plaques (p=0.001), whereas the reduction of the SUM-score was 19% (p =0.10) in the plaques treated with calcipotriol/betamethasone dipropionate. A more detailed description of the clinical results has been reported elsewhere.[15]

T-cell subsets

Dermis. In the dermal compartment, statistically significant reductions of T-cell subpopulations were observed for both treatments after the active treatment period (week 4). At week 4, there were no statistical significant differences between the treatments. After 8 weeks of follow-up, statistically significant higher reductions of CD3+ (70% vs. 34%; p <0.01), CD4+ (68% vs. 27%; p <0.05), CD45RO+ (69% vs. 24%; p <0.05) and CD2+ (66% vs. 22%; p <0.05) T cells were observed for PDL compared with calcipotriol/betamethasone dipropionate therapy. In other words: the anti-T-cell effect in de PDL-treated plaques further reduced, whereas T-cell accumulation in the calcipotriol/betamethasone dipropionate treated plaques stabilized after follow-up (figure 1).

Epidermis. Additionally, epidermal T-cell subsets significantly declined towards week 4 during both treatments. The reductions by both treatments did not show statistically significant differences. However, after the 8-week follow-up period the PDL-treated plaques showed significantly higher reductions of CD3+ (84% vs. 42%; p <0.01), CD8+ (88% vs. 46%; p <0.01), CD45RO+ (89% vs. 35%; p <0.05), CD2+ (86% vs. 59%; p <0.05) and CD25+ (89% vs. 26%; p <0.01) T-cell subpopulations in comparison to the plaques treated with topical calcipotriol/betamethasone dipropionate ointment (figure 2).

NK-T cells

Dermis. During and after treatment, both CD94+ and CD161+ cells in the dermis showed a tendency of reduction compared to baseline. At week 12, no statistical significant difference was observed between the treatments (figure 1).

Epidermis. Low numbers of CD94+ and CD161+ cells were quantified in the epidermis and did not significantly reduce during either treatment modality, neither at week 4, nor at week 12. There were no differences between the treatments (figure 2).

Epidermal parameters

Epidermal proliferation. The mean number of Ki67+ nuclei was significantly reduced at week 4 during each treatment, but the difference between both treatments was

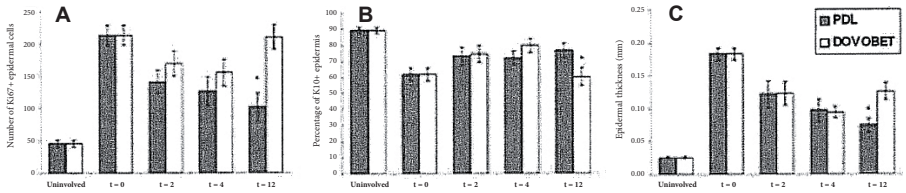

Figure 3. (A) Epidermal proliferation (number of Ki67+ epidermal cells); (B) epidermal differentiation (percentage of K10+ epidermis); and (C) epidermal thickness (mm) during treatment with PDL and calcipotriol/betamethasone dipropionate ointment, at baseline, after 2 and 4 weeks of treatment, and after an 8-week follow-up period.

not statistically significant. At week 12, in contrast, PDL-treated plaques showed a statistically significant lower mean number of Ki67+ nuclei than the plaques treated with topical calcipotriol/betamethasone dipropionate (53% vs. 2% reduction from baseline; p <0.001) (figure 3A).

Epidermal differentiation. The mean percentage of K10+ epidermal area was significantly increased at week 4 during both treatments. After 8 weeks of follow-up, a superior improvement was observed for the PDL-treated plaques compared with calcipotriol/betamethasone dipropionate ointment (24% vs. -3% improvement in K10+ epidermal area from baseline; p <0.001) (figure 3B).

Epidermal thickness. The thickness of the epidermis showed a 59% reduction for PDL-treated plaques and a 31% reduction for the plaques treated with calcipotriol/bethametasone dipropionate, respectively, at week 12 (p <0.001) (figure 3C).

DISCUSSION

In the present study, generally improvements were observed for PDL treatment for activated memory effector T cells, already after 2 and 4 weeks of treatment. A similar response was noticed for the topical treatment with calcipotriol/betamethasone dipropionate. However, after an 8-week follow-up period, dermal CD3+, CD4+, CD45RO+, CD2+ T cells, epidermal CD3+, CD8+, CD45RO+, CD2+, CD25+ T cells, epidermal proliferation (Ki67), and epidermal thickness further reduced and keratinization (K10) improved, in the PDL-treated plaques, but not in the calcipotriol/betamethasone dipropionate treated plaques. These differences were statistically significant.

A tortuous capillary bed, elongation of the rete ridges, hyper- and parakeratosis of the epidermis and the influx of immunocytes in the dermis and epidermis are histological hallmarks of psoriasis.[19,20] Recent insights have mainly pointed towards a potential initiating role for T cells in the pathogenesis of psoriasis.[21,22] However, there is some evidence that microvascular changes occur well before overt T-cell

infiltration and epidermal hyperplasia in the process of formation of a psoriatic plaque.[3-5] Therefore, it may be hypothesized that destroying the diseased capillaries helps preventing T cells to extravasate into the skin. In turn, this might be a reason for the long-standing therapeutic effect of PDL in psoriasis and the observed prolonged immunohistochemical and clinical improvements.

The results of the present study are greatly in line with our previous report on clinical efficacy of the PDL versus treatment with calcipotriol/betamethasone dipropionate ointment.[15] All immunohistochemical effects preceded the clinical effects. With respect to the dynamics of T-cell subpopulations during PDL and treatment with calcipotriol/betamethasone dipropionate the present results are in line with studies reported by Hern *et al*. (PDL) and Vissers *et al*. (calcipotriol and betamethasone dipropionate), although there are some discrepant outcomes as well.[8,16] In the present comparative study, the most intriguing finding in the PDL-treated plaques is the highly reduced number of T-helper cells (CD4+) in the dermis and cytotoxic T cells (CD8+) in the epidermis, memory effector T cells (CD45RO+) and T cells with markers of activation (CD2, CD25). Previously, Hern *et al*. reported a reduction of CD4+ and CD8+ T cells restricted to the psoriatic dermis.[8] However, the study design included only 2 weeks of follow-up, which might have been too short. Cells expressing NK-receptors CD94 and CD161 did not show different responses to PDL and calcipotriol/betamethasone dipropionate ointment therapy in the present study. Also GITR-expressing cells (up-regulated and inhibitory on regulatory T cells) were very few in number and did not show differential responses to both treatments. Conversely, Vissers *et al*. observed a reduction of CD94+ and CD161+ NK-T cells in the dermis after combined treatment with calcipotriol ointment, once daily, and betamethasone dipropionate ointment, once daily.[16] There are no comparable studies for the two-compound formulation of the ointment used in our study.

In the present study, the degree of response to therapy was at variance. It appeared that four of the seven evaluated patients, those patients with complete clearance at week 12, could be determined as 'responders'. Responder patients showed far more normalization of epidermal thickness, proliferation and differentiation, together with a significantly more reduced T-cell infiltrate, than those patients that did not completely respond to PDL. Interestingly, it was observed that a reduction of epidermal T-cell subsets correlated best to overall reduction of plaque severity. This is in line with earlier studies.[23-25] Apparently, normalization of keratinocyte behavior and the observed reduction of epidermal T cells are indirect results, secondarily caused by an inhibited extravasation of dermal T cells due to selective photothermolysis of the diseased psoriatic capillaries by PDL treatment. Indeed, after long term follow-up the clinical and immunohistochemical effect of PDL was still persistent and ongoing. A negative feature was the drop-out of one patient due to pain experienced during and after PDL treatment.

Unfortunately, we have no immunohistochemical data on even longer follow-up duration. Nevertheless, clinical observations even after 1 year of follow-up of responder patients still showed marked improvements of the treated plaque.[15] Indeed, recent studies on PDL for psoriasis indicate response rates between 57% and 82%, and remission may extend up to 15 months.[26] We have to disclose some minor shortcomings: the selection of 'recalcitrant' psoriatic patients; pre-treatment with 10% salicylic acid in white vaseline, which has recently been proven beneficial for the treatment of psoriasis with PDL;[27] an expected higher compliance of PDL versus calcipotriol/betamethasone dipropionate treatment; and the low number of treated patients.

In summary, an evaluation 8 weeks after a 4-week treatment course with PDL for localized and recalcitrant plaque psoriasis resulted in persisting reductions of activated T-helper cells in the dermis and cytotoxic T cells in the epidermis, together with normalization of epidermal proliferation, differentiation and epidermal thickness, well beyond the improvement achieved with topical calcipotriol/betamethasone dipropionate ointment.

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ABSTRACT

Objective: The purpose of this study was to achieve a validated clinical and image scoring system for a single chronic discoid lupus erythematosus (CDLE) lesion.

Methods: Fifteen patients with a CDLE lesion were scored twice by four observers and clinical photographs were taken. These pictures were assessed by the same four observers at two time points. Patients were scored using the DLE-Skin Score (DLE-SS). In addition, the DLE-Photo Score (DLE-PS) was calculated. Statistical analysis was carried out by measuring inter- and intra-observer agreement for both methods and by measuring the correlation between the DLE-SS and DLE-PS.

Results: Both the DLE-SS and DLE-PS proved reliable methods in the assessment of CDLE. The inter-observer variability of the DLE-SS and DLE-SS was low. The intra-observer. Variability was estimated to be 0 in both methods. The correlation coefficient between the DLE-SS and DLE-PS was high (0.81).

Conclusion: Both the DLE-SS and the DLE-PS are reliable and easy-to-use methods to score disease activity in CDLE patients, and can be used in monitoring single target lesions in clinical trials.

Validation of clinical and image skin scoring systems for a single chronic discoid lupus erythematosus lesion

INTRODUCTION

Chronic discoid lupus erythematosus (CDLE) is a skin disorder, which consists of well-defined erythematous, scaly plaques that tend to heal with scarring, atrophy and pigmentary changes. These changes can be very disfiguring; therefore, evaluation of therapy and development of more effective new treatments are important. CDLE is the most common form of cutaneous lupus and is in most cases restricted to the skin only. Approximately 5% of the patients first diagnosed with CDLE later show systemic involvement and are diagnosed as having systemic lupus erythematodes (SLE).[1,2] To monitor the effects of therapy in patients with CDLE, determination of the skin lesion status is necessary.

In most trials or reports in which the effect of new topical or surgical treatments for CDLE is measured, the investigators usually treat one single target lesion.[3-7] To evaluate these new treatment modalities a detailed description of this single lesion is required. Therefore, a simple validated scoring system that focuses on a single lesion is important. The well-developed Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) measurement instrument[8] is very extensive and not focused on one single lesion.

In this study, a new scoring system for CDLE has been designed in which all prominent features, namely erythema (E), induration (I), scaling (S) and atrophy (A), are represented and scored separately, in a detailed way; the sum of these is called the DLE-Skin Score (DLE-SS). Because of the fact that induration cannot be measured from a picture and photograph images are often used in clinical trials, we designed a modified scoring system for the photographed lesions: the DLE-Photo Score (DLE-PS).

Both scoring methods (DLE-SS and DLE-PS) were validated for their concordance between observers and within observers and the degree of agreement between skin score and photo score was calculated.

PATIENTS AND METHODS

Patients

All patients with a histologically confirmed CDLE who had visited the Department of Dermatology at the St Radboud University Hospital over the past 2 years were

Table 1. DLE-SS = Σ(E + I + S + A). DLE-PS = Σ(E + S + A).

Erythema (E)	0 = none
	1 = mild (light red)
	2 = moderate (red)
	3 = severe (very red)
	4 = very severe (extremely deep red)
Induration (I)	0 = none
	1 = slight (slightly increased compared with normal surrounded skin)
	2 = moderate (easily palpable elevation)
	3 = marked (definitely elevated lesions with hard, sharp edges to plaques)
	4 = very marked (elevation with very hard, sharp edges to plaque)
Scaling (S)	0 = none
	1 =mild
	2 = moderate
	3 = severe
	4 = very severe
Atrophy (A)	0 = none
	1 = mild: barely noticeable
	2 = moderate: coarser, noticeable
	3 = severe: thick, shiny, visually obviously
	4 = very severe: high level of disfigurement

contacted by means of a letter. The voluntarily responding patients (33%) were included in the study. To be eligible for the study, patients had to have at least one CDLE lesion.

A total of 15 patients (six men and nine women) participated in this study. The duration of the CDLE ranged from 14 months to 22 years. The number of lesions varied from one single lesion to nine lesions. In case of multiple lesions, the most prominent lesion was selected.

All patients were scored twice in a randomly distributed order at a 1-hour interval by four independent observers: two consultant dermatologists, one chief resident and one junior resident in dermatology. During this visit clinical photographs were taken. These pictures were assessed by the same four independent observers a month after the initial visit and 1 week later for the second time.

Clinical score

The DLE-SS is a cumulative measure which includes scores for erythema (E), induration or plaque thickness (I), scaling (S) and atrophy (A) on a 5-point-scale ranging from 0 to 4 (see table 1).

The DLE-SS is calculated as Σ(E + I + S + A). This scoring system is partially based on the scoring method which Heffernan *et al*. used in their study[3] and extended with a scaling score. The possible minimum score is 0, representing no affected skin, and the maximum score is 16.

Table 2. Percentage of total variance from observers, repetition, patients and random error.

Variance (% of total)	DLE-SS	DLE-PS
Variance from patients	80	86
Variance from observers	6	2
Variance from repetition	0	0
Variance from random error	14	12

Photograph score

Photographs were taken of the scored lesions, using a Nikon D1 105 digital camera under standardized conditions. After one month the photographed lesions were scored by the four observers and 1 week later using the same computer.

DLE-PS is the sum of erythema (E), scaling (S) and atrophy (A) using the same five-point scale for these parameters as described in table 1. The DLE-PS is calculated as $\Sigma(E + S + A)$.

Statistical analysis

The DLE-SS and DLE-PS were analysed statistically as follows.

Observer agreement for both methods was analyzed by considering the total amount of variation present in the ratings and estimating the amount of variability from the patients (σ^2_p), the amount of the repeating of measurements (σ^2_r), the amount of the observers (σ^2_o), and the amount of random error (σ^2_e). In a reliable method, the inter-observer variability (variation of clinicians) and the intra-observer variability (variation from repeated measurements) should be low, whereas the variability caused by diversity of patients should be high.

All variances mentioned were estimated with the maximum likelihood variance components estimation procedure of the SAS-package (SAS Institute Inc., Cary, NC, USA). Results for the various sources of variation are presented as the percentage of the total variance ($\sigma^2_p + \sigma^2_o + \sigma^2_r + \sigma^2_e$).

For analysis of correlations between the DLE-SS and DLE-PS, the Spearman correlation coefficient was used.

RESULTS

Fifteen patients (six men and nine women) participated in this study. Their mean age was 50.5 (± 2.37 SEM) years, the youngest was 36 years old and the oldest was 69 years old. The duration of the CDLE lesions ranged from 14 months to 22 years, with a mean of 10.46 (± 2.08 SEM) years. The number of active lesions ranged from one to nine, with a mean of 4.3 (± 1.10 SEM). Most of the scored lesions were located on the face (10), whereas four lesions were on the vertex and one on the back.

Table 3. Spearman correlation coefficients between DLE-SS and DLE-PS (95% confidence interval). Modified DLE-SS = DLE-SS without induration.

	DLE-SS vs DLE-PS	Modified DLE-SS vs DLE-PS
Observer 1	0.81 (0.51-0.93)	0.84 (0.58-0.95)
Observer 2	0.83 (0.55-0.94)	0.90 (0.72-0.97)
Observer 3	0.80 (0.49-0.93)	0.85 (0.60-0.95)
Observer 4	0.79 (0.47-0.93)	0.83 (0.55-0.94)

The percentage of variance from the patients was high: 80% (DLE-SS) and 86% (DLE-PS). This means that the amount of variation from observers, repeated measurements, and random error was low. The inter-observer variability, expressed as the percentage of variance from observers, was 6 (table 2).The intra-observer variability, which is the variation from repetition of measurements by the same observer, was estimated to be 0 (table 2).The inter-observer variability in the scores from the pictures was only 2, and intra-observer variability was estimated as 0.
The correlation coefficient between the DLE-SS and DLE-PS is approximately 0.81. If only erythema, scaling and atrophy of the DLE-SS (modified DLE-SS) were correlated to the DLE-PS, a correlation of 0.86 was found.
The correlations between the DLE-SS (with and without the induration component) and DLE-PS for the different observers are summarized in table 3.

DISCUSSION

To assess disease activity and efficacy of therapy in one single CDLE lesion it is important to use standardized outcome measures that are reliable, clinically meaningful and feasible to use.
Both the DLE-SS and DLE-PS proved reliable methods in the assessment of a single CDLE. The inter-observer variability of the DLE-PS was low, even lower than the inter-observer variability of DLE-SS (2.0 vs 6.0). This slight difference can be explained by the fact that the DLE-PS had one variable less, namely induration. The intra-observer variability was very low in both scores. This low intra and inter-observer variability means that this method can reliably be used by the same observer at different moments and by different investigators as well.
Correlation between DLE-SS and DLE-PS was 0.81. If only the erythema, scaling and atrophy of the DLE-SS (modified DLE-SS) were correlated with the DLE-PS, a correlation of 0.86 was found. It is striking that the absence of the variable induration in the DLE-SS (modified DLE-SS) does not result in a higher correlation coefficient

between DLE-SS and DLE-PS. In the ideal situation, one would expect a correlation of 1. The fact that the correlation coefficient between the two methods is not 1, implies that both methods cannot easily be exchanged and are not identical.

Besides, the high correlation (0.86) between the modified DLE-SS and DLE-PS is partly due to the fact that our patients were photographed under ideal conditions by the same professional photographer. We realise that these conditions are not always accessible in all clinics.

The DLE-SS has a great advantage compared with the DLE-PS as it is obvious that in the DLE-PS the induration cannot be measured. The difference in induration before and after a treatment is an important outcome measure, which is neglected if only photographs are scored.

In conclusion, both the DLE-SS and the DLE-PS are reliable and easy-to-use methods to score disease activity in CDLE patients. We prefer, however, the DLE-SS, because this method also measures induration, which is a key feature in disease activity. In trials and reports in which one initial target lesion is used as an outcome measure, the DLE-SS and the DLE-PS are very suitable validated methods.

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ABSTRACT

Background: Treatment of chronic discoid lupus erythematosus (CDLE) with a pulsed dye laser (PDL) has shown promising results, although outcomes in previous studies were not validated and laser parameters were inconsistent.

Objective: We conducted an open prospective study to assess the efficacy and safety of PDL for the treatment of recalcitrant CDLE, using a validated scoring method and a fixed treatment schedule.

Methods: Twelve patients with active CDLE lesions were treated with PDL (585 nm, fluence 5.5 J/cm^2, spot size 7 mm) 3 times with an interval of 6 weeks followed by a 6-week follow-up period. Treatment outcomes were evaluated by 3 observers using the validated Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI). Cosmetic results and adverse events were recorded.

Results: A significant decline in ''active'' CLASI was observed after 6 weeks, after 12 weeks, and at follow-up. Baseline active CLASI was 4.4 6 0.2 (mean ± SEM), reaching 1.3 ± 0.3 after follow-up (p <.0001). Individual scores for erythema and scaling/hypertrophy significantly declined 6 weeks after treatment. The ''damage'' CLASI (dyspigmentation, scarring, and atrophy) did not show any significant change during or after therapy. The observed clinical improvement was confirmed by two independent observers by clinical assessment of photographs (r = 0.87 and r = 0.89; both p <.05). The treatment was well tolerated, only minimal pain was reported, and the cosmetic result was fair.

Limitations: Small sample size and short follow-up duration were limitations.

Conclusion: PDL treatment is an effective and safe therapy for patients with refractory CDLE.

Efficacy and safety of pulsed dye laser treatment for cutaneous discoid lupus erythematosus

INTRODUCTION

Chronic discoid lupus erythematosus (CDLE) is characterized by well-defined erythematous, infiltrated, scaly patches. It is the most common form of cutaneous lupus erythematosus and restricted to the skin, mostly in the facial area. As lesional skin heals with scarring, patients are frequently offered camouflage therapy for the residual plaques. Because of its chronicity, CDLE severely affects quality of life.[1-3] Current treatment options include topical and systemic glucocorticosteroids,[4-6] sunscreens,[7] antimalarial agents,[8,9] retinoids,[10,11] dapsone,[12] methotrexate,[13] thalidomide,[14] immunoglobulins,[15] azathioprine,[16] and cyclophosphamide.[17] Occasionally, beneficial effects of topical immunomodulators,[18,19] biologicals,[20,21] cyclosporin,[22] immunoglobulins,[23] mycophenolate mofetil,[24] rituximab,[25] and anti-tumor necrosis factor alfa agents[26] have been reported. When a lack of efficacy or adverse events is experienced,physical and surgical therapies including cryotherapy, dermabrasion, and laser treatment have been tried. Few controlled prospective studies have been performed.

Laser treatment for CDLE was reported for the first time in 1986 by Henderson and Odom.[27] One patient was treated with a carbon-dioxide laser and dramatic improvement was observed. Unfortunately, hypopigmentation and reactivation of CDLE in the treated areas were reported as side effects. In 1988, Zachariae *et al*.[28] treated 5 patients with CDLE with an argon laser, with significant blanching of the lesion although scarring and hypopigmentation were reported after treatment.

Treatment with the pulsed dye laser (PDL) was for the first time described in 1996 by Nuñez *et al*.[29] Telangiectatic chronic erythema was treated in 4 patients with systemic lupus erythematosus by PDL. Treatment of a CDLE lesion with PDL was first reported in 1997 by Maushagen-Schnaas and Raulin.[30] They described total clearance in one patient with CDLE and one with cutaneous lesions in systemic lupus erythematosus. In a retrospective study, Raulin *et al*.[31] reported average clearance of about 70% in 10 patients with CDLE and two with systemic lupus erythematosus in combination with discoid lesions after treatment with PDL. Only in two patients was hyperpigmentation observed. A similar retrospective study in which 14 patients were treated reported a clearance rate of 60%.[32]

To examine the efficacy of the PDL in the treatment of CDLE we designed a prospective open label study in which patients with CDLE were treated with a single laser device and with consistent laser parameters in a fixed treatment schedule. Clinical outcomes were measured by means of a well-validated scoring system.[33-35]

METHODS

Patients

Patients with histologically confirmed CDLE who visited our Department of Dermatology from January 1, 2006, through October 31, 2006, were contacted by postal mail. To be eligible for the study, patients had to have at least one active CDLE lesion, despite the treatment with at least one standard therapy (eg, topical or systemic steroids, antimalarial drugs). All patients were allowed to continue systemic medication for CDLE, provided that this was not started or altered in the past 6 months (table 1). For topical treatment a wash-out period of 2 weeks was set. Exclusion criteria were: age younger than 18 years, pregnancy, lactation, and a history of photosensitivity. This study was approved by the medical ethics committee. Written informed consent was obtained from all patients.

Study design

At baseline one prominent CDLE lesion was selected as the target lesion and prepared for laser treatment. Two weeks before the start of the study, petroleum jelly was prescribed for all patients to standardize and optimize the pretreatment situation. If a lesion still showed scaling at the treatment session, arachis oil was applied to reduce the amount of scattering. The whole lesion was then treated with the PDL (Photogenica V laser, Cynosure, Chelmsfort, CA). Comparing all previous studies with different fluences, spot sizes, and time intervals between two treatments, the best results were achieved with a fluence of 5.5 J/cm^2, a spot size with a diameter of 7 mm, and a treatment interval of 6 weeks.[31] These laser parameters were used as standard treatment for all included patients. A pulse duration of 0.45 ms and a wavelength of 585 nm was constantly used, with one pass and an overlap of 10% to 20% per shot. During and shortly after laser treatment a cooling device (Cryo 5, Zimmer Electromedizin, Neu-Ulm, Germany) was used to reduce pain. If necessary, a second and third treatment was performed 6 and 12 weeks after the initial treatment, respectively. After the treatment period of maximal 12 weeks all patient entered a 6-week follow-up period.

Clinical assessments

Clinical efficacy was assessed at baseline, after 6 and 12 weeks, and at the end of the 6-week follow-up period using the recently validated Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI).[33-35] In brief, this instrument has separate scores for activity and damage of cutaneous lupus erythematosus lesions at 13 different anatomic sites.

As one single CDLE lesion was assessed, which in almost all patients was located on the face, measuring the area of involvement was not relevant. Hence, a ‘‘limited’’ CLASI

scoring system was used, subdivided into an ''active'' and ''damage'' component. The limited active CLASI for just one target lesion included the degree of erythema (ranging from 0 = absent to 3 = dark red/purple) and scaling/hypertrophy (ranging from 0 = absent to 2 = verrucous/hypertrophic). The addition of these scores resulted in a total limited active CLASI score of the concerning lesion, ranging from 0 to 5. The limited damage CLASI was determined by measuring the presence of dyspigmentation (0 = absent or 1 = present) and scarring/atrophy/panniculitis (ranging from 0 = absent to 2 = severely atrophic scarring or panniculitis). The addition of both resulted in a maximum damage score of 3. The total limited CLASI reflected the sum of both active and damage CLASI, resulting in a score ranging from 0 to 8. All patients were evaluated by the same investigator at baseline and at subsequent visits.
Adverse events were recorded and patients reported pain and the cosmetic result on a visual analog scale (VAS). VAS scores were assessed after every PDL treatment and at follow-up. A score of 0 represented a total absence of pain and a cosmetically fully unsatisfactory result after treatment, whereas 10 represented maximal pain and a cosmetically excellent result after all treatments, respectively.

Photographic evaluation

At every visit clinical photographs of the target lesions were made. Pretreatment and posttreatment photographs were evaluated by two additional independent dermatologists using the CLASI.

Statistical analysis

All analyses were carried out using statistical software (Statistica, Version 6.0, Statsoft Pacific, Melbourne, Australia). One-way analyses of variance were performed to study the clinical scores and their changes over time. If significant, Duncan's post hoc comparison test was carried out. Interindividual correlation was determined by measuring Pearson correlation coefficient *r*. A *p* value of less than 0.05 represented the presence of a statistically significant difference.

RESULTS

Patient characteristics

Twelve patients (5 men and 7 women) with mean age of 52.8 ± 2.8 (mean ± SEM) years were included. The mean duration of CDLE lesions was 11.2 ± 2.1 years. The number of active lesions ranged from one to nine. Ten of the treated lesions were located on the head, whereas one lesion was located on a left arm and one on a back, respectively. Patient characteristics are detailed in table 1.

Table 1. Patient characteristics and treatment outcomes CLASI, cutaneous lupus erythematosus disease area and severity index; F, female; M, male; od, once daily.

Patient	Sex	Age, y	Location	Concomitant treatment	No. of sessions	Active limited CLASI				Damaged limited CLASI				Side effect
						Baseline	6 wk	12 wk	End follow-up	Baseline	6 wk	12 wk	End follow-up	
1	M	69	Nose	None	3	4	4	2	2	1	1	1	1	None
2	M	55	Scalp	None	3	3	1	0	0	2	2	2	2	None
3	M	66	Scalp	Hydroxychloroquine 100 mg od	3	4	3	3	1	3	1	1	2	None
4	F	67	Nose	Hydroxychloroquine 200 mg od	3	5	3	3	2	2	1	1	2	None
5	F	54	Forehead	Hydroxychloroquine 200 mg od	3	5	2	2	2	3	3	3	3	None
6	M	37	Lip	Hydroxychloroquine 200 mg od	1	3	0	0	0	1	0	0	1	None
7	M	48	Back	Prednisone 5 mg od and azathioprine 100 mg twice daily	3	5	1	1	1	2	2	2	2	None
8	F	46	Nose	Hydroxychloroquine 200 mg od	3	5	2	2	2	1	0	0	0	None
9	F	46	Scalp	Hydroxychloroquine 200 mg od and prednisone 5 mg od	3	4	3	3	3	1	1	1	1	None
10	F	52	Cheek	Prednisone 7.5 mg od and azathioprine 150 mg od	3	5	4	3	3	1	2	2	2	None
11	F	50	Arm	None	3	5	0	0	0	1	1	1	1	Slight hyperpigmentation
12	F	44	Cheek	Prednisone 7.5 mg od and methotrexate 20 mg once weekly	3	5	3	4	0	0	0	0	0	None
Mean		52.8				4.4	2.2	1.9	1.3	1.3	1.3	1.3	1.3	

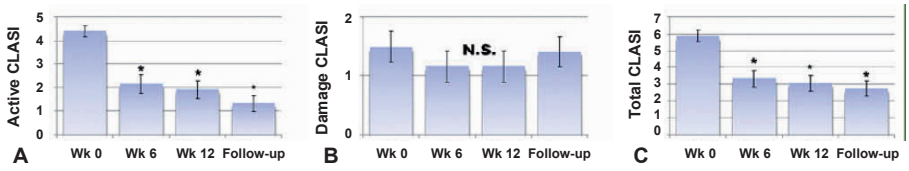

Figure 1. Active (A), damage (B) and total (C) Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) at baseline, week 6, week 12, and after 6-week follow-up (mean ± SEM). N.S., Not significant. *Statistically significant compared with baseline.

Active CLASI

Most patients showed a significant improvement of the treated lesion resulting in a decrease of the limited active CLASI (mean ± SEM). At baseline the limited CLASI was 4.4 ± 0.2. Six weeks after the initial treatment the CLASI declined to 2.2 ± 0.4 (p =.0002). At week 12 and after a 6-week follow-up period, CLASI was 1.9 ± 0.4 and 1.3 ± 0.3, respectively (p <.0001) (figure 1A). The separate score for erythema and desquamation significantly reduced from 2.9 ± 0.1 to 0.9 ± 0.2 (p <.0001) and from 1.5 ± 0.2 to 0.4 ± 0.2 (p =.007), respectively.

Damage CLASI

In contrast, the damage CLASI neither showed any significant improvement during nor any worsening after 6 weeks, after 12 weeks, and at follow-up. Damage CLASI was 1.5 ± 0.3 at baseline and 1.2 ± 0.3 at the end of the study. After follow-up the score was 1.4 ± 0.3 (p =.74) (figure 1B).

Total CLASI

Despite the damage CLASI not being affected, the total CLASI (active + damage CLASI) yielded a highly significant amelioration: 5.9 ± 0.3 at baseline to 3.1 ± 0.5 directly after treatment (p =.0001) and 2.8 ± 0.5 after follow-up (p <.0001), respectively (figure 1C).

Interobserver correlation

The active CLASI correlated very well with the scores derived from two blinded separate observers. Photographs were scored and yielded a correlation of r = 0.87 and r = 0.89 (both p <.05) for the two independent observers as compared with the initial clinical scores, respectively. The two photograph observers intercorrelated well with r = 0.96 (p <.05).

Adverse events and cosmetic result

Patients reported minimal pain. The overall pain score, as measured on a 0-to-10 VAS, was only 2.4 ± 0.5 (mean ± SEM). Only one patient (8%) developed slight

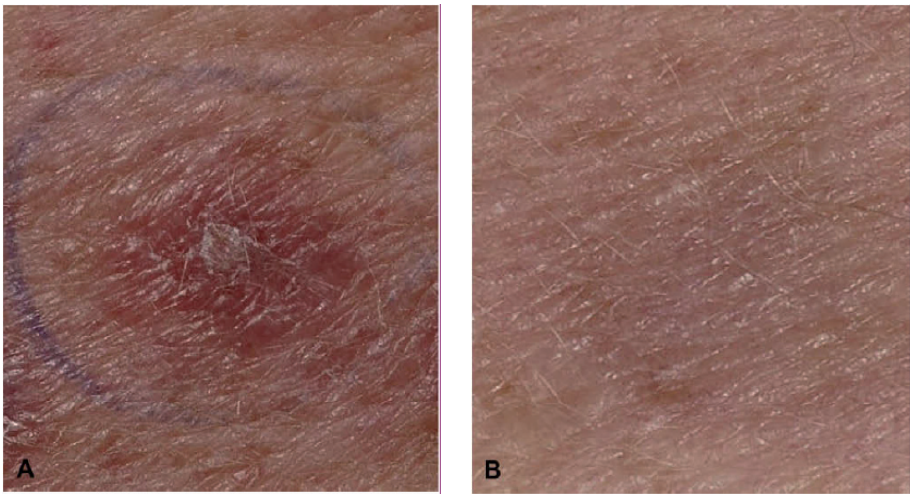

Figure 2. Chronic discoid lupus erythematosus lesion of patient before (A) and after (B) pulsed dye laser treatment, showing slight hyperpigmentation.

hyperpigmentation after PDL treatment (figure 2). However, the patient-rated overall cosmetic result, as measured on a 0-to-10 VAS, was a fair 6.9 ± 0.5 (mean ± SEM).

DISCUSSION

Treatment of CDLE lesions with a PDL showed promising results in the case reports and retrospective studies described in our introduction.[27-32] In these studies the number of treatments varied from one single treatment up to 10. There was also a wide variation in laser parameters such as spot size (diameter 3-7 mm), energy fluence (3-13 J/cm^2), and pulse duration (0.3-0.45 ms). In one study, different laser systems were used.[32] The results were obtained by determining the so-called clearance rate from clinical photographs taken before and after treatment. This method, however, is not a validated measurement instrument for CDLE lesions.

In this study, a prospective design was chosen to treat CDLE lesions with PDL, with a fixed treatment schedule and validated measurements (CLASI).[33-35] A significant decline in active CLASI was observed during and after treatment. Separate individual scores for erythema and scale/hypertrophy significantly declined 6 weeks after treatment. On the other hand, scores for dyspigmentation and scarring/atrophy/panniculitis (damage CLASI) did not show any significant improvement. The observed clinical improvement was confirmed by assessment of photographs taken before and after treatment by two independent observers. The treatment was well tolerated

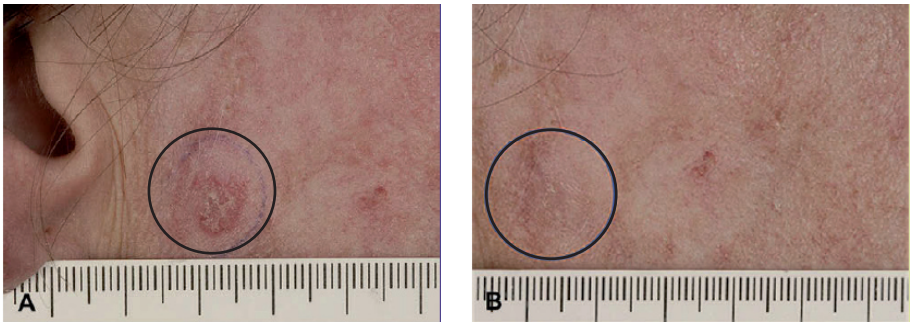

Figure 3. Clinical photograph of target chronic discoid lupus erythematosus lesion of patient 12, before (A) and after (B) pulsed dye laser treatment follow-up.

and no serious side effects were noted. Only minimal pain was reported and the patient-rated overall cosmetic result was fine. A clinical photograph before and after 6 weeks of treatment is depicted in figure 3. At this time, no scarring or relapses have been observed in our patients.

As expected, the damage CLASI was unaffected after treatment. This is well explained by the fact that the suggested working mechanism of the PDL (selective photothermolysis) results in a selective destruction of the cutaneous microvasculature. This may modulate the inflammatory network leading to regression of concerning CDLE lesions.[36] Therefore, PDL treatment may affect the active CDLE lesion, but not, or only to a lesser extent, the damage components. Serial skin biopsy studies may shed light on the effects of PDL treatment on the pathophysiology of CDLE lesions.

Correlations between the scored CLASI by 3 independent observers were 0.87 and 0.89, which is exceptionally high. This means that both the clinical assessment and the assessment of the photograph taken from the target lesion are interchangeable.

Importantly, this study offers 3 relevant novelties. First, standardized laser parameters of a single laser device for the treatment of one single stable CDLE lesion were used. These standardized parameters induced excellent clinical results; therefore, individual adjustments do not seem obligatory for good clinical effects. Also, if necessary, the same interval between the treatments was maintained. Second, a recently validated measurement instrument for clinical trials on cutaneous lupus erythematodes was used (CLASI). This scoring method measures both severity and area involvement of cutaneous lupus erythematodes. Because we treated only one single CDLE lesion, we did not use the area involvement component, and showed that this scoring method is applicable for the follow-up of severity of one single CDLE lesion. This application can be used in the future for evaluation of new topical or physical treatments, where multiple lesions and one target lesion is treated. Third, clinical improvement was confirmed by two additional independent dermatologists, by examining the photographs taken before and after treatment.

Limitations of this study are the relatively small patient group and the short follow-up period. It would be worthwhile to evaluate the effect of PDL in a larger group of patients. Nevertheless, significant clinical improvements were detected; hence PDL may be an important addition to the therapeutic armamentarium for the treatment of CDLE. Future studies can be conducted, varying the parameters (eg, pulse duration and fluence), which may result in even more efficacious treatment with fewer side effects, such as hyperpigmentation.

In conclusion, PDL treatment is an effective and safe therapy for patients with refractory CDLE. PDL treatment may be considered for the treatment of stable, solitary, active CDLE lesions, when topical and/or systemic therapies have failed or are contraindicated.

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Present position of the pulsed dye laser

4

4.1 The efficacy of pulsed dye laser treatment for inflammatory skin diseases: a systematic review

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ABSTRACT

Background: The position of the pulsed dye laser (PDL) in the treatment of inflammatory skin diseases is still unclear. Evidence based recommendations are lacking.

Objectives: We sought to systematically review all available literature concerning PDL treatment for inflammatory skin diseases and to propose a recommendation.

Methods: The authors searched for publications dated between January 1992 and August 2011 in the database Pub Med. All studies reporting on PDL treatment for an inflammatory skin disease were obtained and a level of evidence was determined.

Results: Literature search revealed 52 articles which could be included in this study. The inflammatory skin diseases treated with PDL consisted of: psoriasis, acne vulgaris, lupus erythematosus, granuloma faciale, sarcoidosis, eczematous lesions, lichen sclerosis, granuloma anulare, Jessner lymphocytic infiltration of the skin, reticular erythematous mucinosis and papulopustular rosacea. The efficacy of PDL laser treatment for these inflammatory skin diseases was described and evaluated.

Limitations: Most conclusions formulated are not based on randomized controlled trials.

Conclusions: PDL treatment can be recommended as an effective and safe treatment for localized plaque psoriasis, as well as for acne vulgaris (recommendation grade B). For all other described inflammatory skin diseases PDL seems to be promising, although the level of recommendation did not exceed level C.

The efficacy of pulsed dye laser treatment for inflammatory skin diseases: a systematic review

INTRODUCTION

The flash lamp pumped pulsed dye laser (PDL) was the first laser specifically developed for the treatment of vascular lesions. The mode of action of the PDL is based on the principle of selective photothermolysis,[1] a targeted damaging of specific structures in the skin without damaging the surrounding area and by direct cutaneous immunological activation.[2,3] Omi *et al.*[2] have shown acute inflammatory changes (neutophils, monocytes and mast cells) three hours after laser treatment and four weeks later many lymphocytes and fibroblasts were observed, still increasing in week five, whereas the capillaries showed an almost normal structure at week two.
The current PDL is able to vary the different parameters such as the spot size (up to 12 mm), the pulse duration (ranging from 0.35 to 40 ms) and the energy fluence, which is increased in recent years due to the development of protective cooling systems.[4]
The most frequently used wavelengths are 585 and 595 nm allowing the penetration depth to a maximum of 1.5 mm. So, the fields of application are limited to superficial structures. Side effects during and after treatment with PDL are dependent of the chosen parameters, location and skin type. They include erythema, purpura, edema, blistering, crusting, pigmentary changes and rarely scarring.[5]
Today, the PDL is considered the laser of choice for most congenital and acquired vascular lesions.[6-8] In addition, it is used for the treatment of many other non-vascular or vascular dependent indications, like viral infections[9,10], scars[11] and stretch marks.[12]
In 1992 Hacker *et al.* described for the first time the treatment of an inflammatory skin disease, psoriasis, with the pulsed dye laser.[13]
In order to examine the position of the PDL for the treatment of inflammatory skin diseases, we reviewed the current literature and provided updated information on the treatment of inflammatory skin diseases with the PDL.

METHODS

The focus of attention was the use of PDL in patients with inflammatory skin diseases. The authors searched for peer reviewed publications dated between January 1st 1992 and August 31th 2011 in the computerized bibliographic database Pub Med. Selected languages were limited to English, German and Dutch. The key terms used were pulsed dye laser and pulsed dye lasers. The term ”inflammatory skin diseases” includes an extensive range of different diagnoses. Therefore the whole literature

Table 1. Level of evindence.

1a	Systematic review of RCTs
1b	Individual RCT
2a	Systematic review of cohort studies
2b	Individual cohort study (including low-quality RCT)
3a	Systematic review of case control studies
3b	Individual case control study
4	Case series
5	Case reports, expert opinion

RTC, randomized controlled trial; Data from the Oxford Center for Evidence-based Medicine Levels of Evidence.[15]

on PDL was systematically scanned by a dermatologist, to be sure that all possible inflammatory skin diseases were found. Full details upon the search strategy are available upon request.

Exclusion criteria were: treatment of lesions other than inflammatory skin diseases, the use of other laser systems than the PDL and the use of concomitant local therapies, except for pre-treatment with keratinolytics in order to reduce scale and enhance PDL penetration. The use of concomitant systemic therapy was allowed, if this was not started or altered more than six weeks prior to the study onset or during the study itself. Outcome measures depended on the investigated skin disease. Because the available literature about PDL for inflammatory skin diseases is limited, all found articles were reviewed, including case-reports, case-series, retrospective studies, open-label trials, and randomized controlled trials. The bibliographies of all articles identified were checked for additional relevant articles that were not identified in the Pub Med search. After the initial search was preformed, all abstracts were screened for suitability for inclusion. Full text of the suitable abstracts were obtained. Articles were assigned a level of evidence (LOE) and afterwards graded according to the "Oxford Centre for Evidence-based Medicine Levels of Evidence"[14] (table 1 and 2) by three dermatologist.

RESULTS

Trial flow

In total 2215 articles regarding pulsed dye laser were identified. After screening of titles, abstracts, and full text articles if applicable, fifty-two of these articles were suitable to be used in the review. The publications of the inflammatory skin diseases treated with PDL consisted of: psoriasis (13), acne vulgaris (9), lupus erythematosus

Table 2. Grades of recommendation.

A	Studies with consistent LOE 1a and/or 1b
B	Studies with consistent LOE 2a, 2b, 3a, or 3b;or extrapolations from studies with LOE 1a or 1b
C	Studies with LOE 4 or extrapolations from studies with LOE 2a, 2b, 3a, or 3b
D	Studies with LOE 5 or troubling inconsistent or inconclusive studies of any level

LOE, level of evidence; Data from the Oxford Center for Evidence-based Medicine Levels of Evidence.[15]

(including systemic lupus erythematosus, chronic discoid lupus erythematosus and subacute cutaneous lupus erythematosus) (8) granuloma faciale (7), sarcoidosis (5), chronic eczema (1), lichen sclerosis (3) granuloma anulare (2), Jessner lymphocytic infiltration of the skin (1), reticular erythematous mucinosis (1) and papulopustular rosacea (2). All results are shown in table 3.

Psoriasis

Literature search revealed eleven articles describing PDL treatment for localized plaque type psoriasis [19,23] localized, chronic stable plaque psoriasis[15,17,18,20] and localized recalcitrant plaque psoriasis[13,16,21,22,24]. In most studies PDL treatment was limited to one single or a few of lesions. Two articles described the treatment of nail psoriasis.[25,26] Outcome measures included clinical scores as (modified) Psoriasis Area and Severity Index (PASI), psoriasis severity index (PSI), Physician's Global Assessment (PGA)[30-31], total plaque severity score for erythema, scaling and thickness, nail psoriasis severity index (NAPSI)[32], and more subjective parameters such as percentage of clearance obtained from pictures taken before and after treatment.

Taibjee *et al*[19] (LOE 2b) published a within-patient controlled prospective trial of treatment of localized plaque psoriasis in 22 patients. Every patient received three different treatments, applicated to three different plaques: PDL treatment with salicylic acid (SA) pretreatment, excimer laser twice weekly and SA alone. One plaque was left untreated to serve as control side. The PDL treated lesions showed complete clearance in 6 patients (27%) and improvement in 15 patients (68%). Clinical response to treatment was significantly greater for PDL than for both SA alone as untreated control. The psoriasis severity index (PSI) showed an significant improvement of PDL treated lesions compared to untreated lesions and there was an improvement compared to SA treated lesions. A subset of patients responded better on the PDL, although the excimer laser appears to be on average more efficacious.

De Leeuw *et al*.[23] (LOE 2b) preformed a single-blind, prospective paired randomized controlled study. In 27 patients four similar psoriasis lesions were divided into two halves and treated with PDL *vs* UVB(1), UVB *vs* no treatment (2), PDL *vs* no treatment (3) and PDL+UVB (4). The Physician's Global Assessment (PGA) score showed a significant

improvement of the psoriasis lesions after both PDL treatment and UVB treatment. No significant differences were noted between the therapies. Hacker *et al*.[13] (LOE3b) treated 20 patients using fluences of 5, 7, and 9 J/cm^2 in three quadrants within one lesion; leaving one quadrant as a control side. In 11 of 19 patients clinical improvement was seen after one session in the area treated with 9 J/cm^2, no improvement was seen in the other areas. Katugampola *et al*.[15] (LOE3b) treated 8 patients with chronic symmetrical plaque psoriasis on one side, using the other side as a control side. Complete clearance was seen in one patient and a reduction of more than 50 % was seen in five patients after three PDL treatments. Another study[16] (LOE3b) including 10 patients, showed a significant decline of psoriasis severity score in 6 patients and minimal advantage in 1 patient after PDL treatment. Zelickson *et al*.[17] (LOE 3b) achieved significant clearance in two to five sessions: In 13 patients one single psoriasis plaque was divided in two and treated unilaterally, leaving the other side as a control side. In another 23 patients the plaque was divided in four quadrants. Different pulse durations (0.45 and 1.5 ms), triamcinolone acetonide 0.1% ointment and an emollients, were used in the separate quadrants. Significant clinical improvement was seen after PDL. Bjerring *et al*.[18] (LOE 4) compared one PDL treatment with dermabrasion in eleven patients. The PDL treated lesions showed a complete response in three patients and a partial response in six patients. Two studies[20,22] (LOE 3b) compared PDL treatment with an active comparator and both studies showed significant reduction of psoriasis after PDL treatment, although the effect compared to the comparator varied in both studies due to the difference in laser parameters and chosen active comparator. Two studies investigated PDL treatment in nail psoriasis[25,26] (LOE 4). One study[26] showed a significant decrease in the Nail Psoriasis Severity Index (NAPSI) score.

Conclusion:

Grade B *for localized plaque psoriasis (two studies with LOE 2B[19,23] and six studies with LOE 3B[13,15-17,20,22]).*

PDL proved to be an effective treatment for localized psoriasis.

Grade D *for nail psoriasis (two studies with LOE 4[25,26])*

No solid conclusion could be drawn for the treatment of nail psoriasis with PDL.

Acne

Literature search revealed nine studies on PDL treatment for acne vulgaris.[34-42] Outcome measures included the Leeds grading system, revised Leeds grading system, acne lesions counting count and percentage of clearance scored on pre and post treatment pictures.[49-52]

Seaton *et al.*[34](LOE 1b) performed a randomized double-blind study in 41 patients with mild-to-moderate facial acne. Twelve weeks after a single PDL treatment, with two different fluences given randomly at each side of the midline, they reported

clinically and statistically significant reduction in acne lesions on both sides of the face. Orringer *et al*.[35] (LOE 1b) did a single-blind split-face RCT in 26 patients. At 12 weeks changes in lesions count were not significantly different for treated *vs*. non-treated sites. A trend towards improvement in inflammatory acne was described. Jasim *et al*.[36] (LOE3b) did a split-face study in 10 patients, in which one half was treated with PDL and the untreated site served as a control side. 50% had visible improvement in their acne on the treated site. Another study[41] (LOE 3b) compared PDL treatment with a regular acne treatments. One group of fifteen patients was treated with PDL, and compared with two groups who received regular topical treatments (topical vitamin A acid, benzoyl peroxide) or chemical peels (trichloroacetic acid (TCA) 25%). Significant decrease in all three groups was seen, although in the follow-up period remission was significantly higher in the PDL group. PDL treatment was also compared to other, less established, treatments for acne[38-40,42] (LOE 4). 15 patients treated in a split face study with long-pulsed PDL in comparison to long-pulsed dye laser assisted photodynamic therapy with methylaminolevulinic acid (MAL-LPDL)[38] showed a reduction for both treatments. Non-inflammatory lesions reduced similar, whereas inflammatory lesions were more reduced on the MAL-LPDL site. In comparison with light emitting diode (LED) and intense pulsed light source (IPL)[39] PDL achieved more than 90 % clearance after 4.1 sessions, compared to 6.0 for IPL and 10.0 for LED. In a comparative study with IPL[42], both devices showed a significant reduction at week 8 compared to baseline; this reduction was significant larger for PDL compared to IPL treated sites. A different study[40] compared PDL with combined 585/1064-nm laser treatment and found a significant reduction for both inflammatory and non-inflammatory lesions, after both treatments.

Conclusion:

Grade B *for acne vulgaris (one study with LOE 1b[34] and two studies with LOE 3B[36,41])*

PDL seems to be an effective treatment for acne vulgaris.

Chronic discoid lupus erythematodes (CDLE), in systemic lupus erythematodes (SLE), subacute cutaneous lupus erythematodes (SCLE) and lupus tumidus (LT)

PDL treatment was given for CDLE lesions (27 patients),[55,56,59,60] for teleangiectasias and erythematous patches in patients with SLE (12 patients),[53,54,55,56,58] for SCLE lesions (3 patients)[56,57,60] and for LT (2 patients).[60] Outcome measures included estimated clearance rate (ECR) and modified cutaneous lupus erythematodes disease area and severity index (CLASI). [61]

CDLE

Raulin *et al*.[56] (LOE 4) described the treatment of 8 CDLE patients in a retrospective

study and showed an average clearance rate of 57.5 % after an average of 4 treatments (ranging from 1-6) One study[59] described a significant improvement of CDLE lesions after PDL treatment. A recently published study[60] confirmed these findings.[57]

Conclusion:

Grade C *for CDLE (3 publications with LOE 4[56,59,60]*).

PDL seems an effective therapeutic option for localized CDLE.

SLE

Nunez *et al*.[54] (LOE 4) described for the first time the treatment of four SLE patients with PDL and found a clearance rate of 75%. Similar results were founded by Baniandres *et al*.[58] (LOE 4) describing an average clearance of 68.0% (range 50-80%) after 4.2 (range 1-10) treatments in five patient. Another case serie[56] (LOE 4) confirmed these findings. One case report[55] (LOE 5) described complete clearance after three PDL treatments.

Conclusion:

Grade C *for SLE (3 publications with LOE 4[54,56,58]).*

PDL seems an effective therapeutic option for SLE.

SCLE and lupus tumidus

Three patients with SCLE (LOE 5)[56.57,60] showed marked improvement after PDL treatment and two patients with lupus tumidus (LOE 5)[60] showed a significant reduction of erythema and scaling after PDL treatment.

Conclusion:

Grade D *for the treatment of SCLE (3 patients) and lupus tumidus (2 patients).*

PDL in SCLE and lupus tumidus seems effective in a small number of patients

Pulsed dye laser in granuloma faciale

The treatment of granuloma faciale (GF) with PDL was described in five case reports[62-68] and two case series.[66,67]

Cheung *et al*.[66] (LOE 4) reported four cases of GF treated with PDL. Two patients achieved a significant cosmetic improvement of their GF, whereas the GF lesions in the other two patients stayed unaltered. No complications were recorded. A recently published case serie[67] (LOE 4) of four patients described complete flattening and bleaching of all treated lesions in three patients, whereas one treated lesion remained bright red-brown. Four case reports[62-65] (LOE 5) described a complete remission of GF after pulsed dye laser treatment, whereas one case report[68] (LOE 5) described a marked improvement.

Conclusion:

Grade C *for granuloma faciale (2 case series with LOE 4[66,67]).*

Treatment of granuloma faciale with PDL seems to be promising, but the number of patients is too small to draw a firm conclusion.

Pulsed dye laser in cutaneous sarcoidosis

Five case reports of PDL treatment for cutanous sardoidosis/lupus pernio[69-73] were identified. An improvement of 75% till complete remission was described in four cases[69,70,72,73]. One case-report described a limited effect.[71]

Conclusion:

Grade D *for cutaneous sarcoidosis (5 case reports with LOE 5[69-73]).*

PDL seems to be an effective treatment to improve cutaneous sarcoidosis lesions, however, a solid conclusion could not be drawn based on 5 patients.

Eczematous skin lesions

One article was found in which chronic eczema were treated with the pulsed dye laser. Syed *et al*.[76] (LOE 3b) treated 12 children with localized chronic eczema with one cycle of PDL in a pilot study. A significant decrease in Eczema Severity Score (ESS) and a significant difference in eczema severity assessed by a visual analogue score (VAS) was found in favour of PDL. The treatment was well tolerated.

Conclusion:

Grade C *for chronic eczema (one study with LOE 3b[76]).*

PDL treatement for eczematous lesions seems to be promising. More studies with larger patient numbers are needed.

Pulsed dye laser in papulopustular rosacea

Two studies for papulopustular rosacea was identified. Berg *et al*.[88] (LOE 3b) treated 14 patients with moderate to severe papulopustular rosacea and marked telangiectases/ erythema with PDL. Ten patients finished the study. After treatment two patients had markedly less papulopustular lesions, three had only slight less papulopustular lesions, in three patients lesions were unchanged, two patients developed more lesions after treatment. Bernstein *et al*.[89] (LOE 4) described significant decrease in rosacea in 17 patients.

Conclusion:

Grade C *for papulopustular rosacea (one study with LOE 3b[88]).*

The use of PDL for papulopustular lesions in rosacea showed controversial results in one study. More studies with larger patient numbers are needed.

Pulsed dye laser in lichen sclerosis, granuloma anulare, Jessner lymphocytic infiltration and reticular erythematous mucinosis (R.E.M.)

Three case reports were found about pulsed dye laser treatment for lichen sclerosus.[80-82] Two case reports[80-81] (LOE 5) described complete clearance of the treated lesions, whereas one report[82] (LOE 5) described a marked improvement in one treated lesion, and a moderate effect in another treated lesion. Two case reports are described about granuloma anulare (GA).[84,85] Both case reports (LOE 5) described an almost complete flattening and lightening of the treated lesions. One case report of Jessner lymphocytic infiltration of the skin.[86] describes a complete clearance after one PDL treatment. One case serie[87] reports complete clearance and good clinical response of R.E.M.in two patients after PDL treatment.

Conclusion:

Grade D *for lichen sclerosis (3 case reports with LOE 5[80-82]), granuloma annulare(2 case reports with LOE 5[84,85]) Jessner lymphocytic infiltration (one case report with LOE 5[86]) and R.E.M.(one case serie with LOE 5[87]).*

The efficacy of PDL is still unclear, due to the small number of treated patients.

DISCUSSION

Initially, the pulsed dye laser was used for the treatment of vascular indications. Two decades ago, the PDL treatment of a psoriasis plaque lesion[14] showed promising results and therefore triggered the attention to optimize the treatment parameters for this disease and to explore pulse dye laser treatment for other inflammatory skin diseases.

Literature concerning treatment efficacy and safety of pulsed dye laser for inflammatory skin diseases is diverse. Overall, most studies have shown limitations in small patient numbers, inconsistent treatment parameters and a relatively short follow up period. Large randomized controlled trials with consistent laser parameters, validated outcome measures and long follow-up period are lacking.

Psoriasis was the most investigated inflammatory skin disease. All studies described the treatment of localized psoriasis, which mostly concerned chronic, stable plaque psoriasis, sometimes explicitly described as recalcitrant, not responding to conventional therapy such as potent topical steroids, UVB, PUVA and tar. The results of treatment with PDL on various sites of the body were highly variable, therefore no recommendation can be done about which anatomic site will respond best. Despite the currency of this skin disease, no large randomized controlled trials on the efficacy of PDL for psoriasis were identified. Practically, PDL treatment is limited for a few

psoriasis plaque lesions who are resistant to conventional therapy. According to our opinion, it should be considered, based on evidence, for solitary recalcitrant psoriasis lesions.

Two large randomized controlled trials[35,36] were preformed for acne treatment with PDL. The statistically significant improvement of acne lesions after PDL treatment in the first study, could not be confirmed by the second study, possibly due to different used laser parameters and different treatment regimens. Despite the positive finding of the first study and the promising results found in other studies, it is still unclear, whether PDL treatment for acne will become a standard treatment in the future. No large intra-patient, split-face comparative studies were done with PDL treatment in comparison with other well established, easy accessible treatments, so the added value to conventional forms of therapy is still unclear. One could hypothesize that it can be an alternative when topical therapies have failed or are contraindicated, before starting systemic therapy. Recommendation grade B was given for the PDL treatment of both localized psoriasis and acne vulgaris.

Evidence for all other in this review mentioned inflammatory skin diseases (SLE, CDLE, SCLE, granuloma faciale, cutaneous sarcoidosis, chronic eczema, lichen sclerosis, granuloma annulare, Jessner lymphocytic infiltration of the skin, REM and papulopustular rosacea) is of a low level, i.e. grade C and D. While the incidence of these skin diseases, except for eczematous lesions and rosacea, is quite low, it is unlikely that large randomized trials will be performed in the near future to position the PDL for these skin diseases. Despite the low recommendation level, it is still worth to consider treating these lesions with PDL, when topical and/or systemic therapies have failed or are contraindicated, while they are often located in the facial area/chest and can be recalcitrant to conventional therapies, therefore giving a lot of emotional distress. Due to the light sensitivity of some of these diseases, one should be extra cautious when treating these lesions with PDL. One study described the treatment of eczema with PDL and showed good results. This promising result should be further investigated, with the emphasis, like in psoriasis, on localized recalcitrant eczema with failure or contra-indication to topical and/or systemic therapies.

Pulsed dye laser treatment for inflammatory skin diseases has shown to be effective for localized psoriasis and acne vulgaris and can be recommended if conventional therapies have failed and/or are contraindicated. For other inflammatory skin it can be considered as an alternative or supplementary treatment. Long-term studies in large groups of patients are clearly needed.

Table 3. CLASI, cutaneous lupus erythematosus disease area and severity index[61]; CR, case report; CS, case series; E, erythema; ECR, estimated clearance rate; ESS eczema severity score[77-79]; H, histological examination; I, infiltration/induration; IPL, intense pulsed light source; LED, light emitting diode; m, month; NAPSI, nail psoriasis severity

Author	LOE	Study type	No. of patients	Laser parameters				Treatment parameters		
				λ	ø	pulse duration	fluence	No. of treat-ments	Treatment interval	Follow-up
Psoriasis										
Hacker *et al.*, 1992 (13)	3b	OL	19	585	5	0.45	5.0,7.0 and 9.0 di-vided over 4 quadrants, leaving one quadrant untreated	1	_	8 w
Katugampola *et al.*,1994 (15)	3b	OL	8	585	5	0.45	8.5	3	2	10 m
Ros *et al.*,1996 (16)	3b	CS	10	585	5	0.36-0.45	6.5-8.0	1-3	2-3w	2-9 w
Zelickson *et al.*,1996 (17)	3b	OL	36	585	5	0.45;1.5	7.5-8.5	2-5	2-3w	4-13 m
Bjerring *et al.*,1997 (18)	4	CS	11	585	5	0.2	2.0-7.0	1	_	4-9 m
Taibjee *et al.*, 2005 (19)	2b	OL	22	595	7	1.5	10.0-12.0	2-4	4w	12 m
Ilknur *et al.*, 2006 (20)	3b	CS	19	585	5	0.35	7.0-8.5	3	3w	9 w
de Leeuw *et al.*, 2006 (21)	4	CS	41	585	7	0.45	5.0-6.5	4.2	4-6w	36 m
Erceg *et al.*, 2006 (22)	3b	OL	8	585	5	0.45	8.5	1-3	2w	3 m
de Leeuw *et al.*, 2009 (23)	2b	OL	27	585	7	0.45	5.5-6.5	4	3w	13 w

index[32]; OL, open label trial; PASI, psoriasis area and severity index[30-31]; PGA-score, physician's global assessment-score[30-31]; P, pictures before and after treatment; PSI, psoriasis activity and severity index; RCT, randomized controlled trial; S, scaling; SA, salicylic acid; T, thickness; VAS, visual analogue score; w, week; y, year.

Location	Control side	Pre-treatment	Tool assessment	Results	Side effects
trunk/sacral/ extremities	one quadrant in lesion	no	E,S and T on 1-7 scale, P	11 (57%) of 19 patients were found to have a clinically positive effect in de quadrant treated with 9.0 J/cm2. no complete clearance. Negliligible improvement in 5.0 and 7.0 quadrant.	none
knee/elbow	yes	emollient	E,S and T on 0-4 scale, PASI, H	5 patients> 50% reduction of plaque severity score, 1 patient had complete clearance ; decrease of vessel diameter. No decernible trend in cell infiltrate (polymorphs and lymphocytes)	hemoragic crusts
arm/leg/trunk	yes	emolllient	E,S and I on 0-3 scale,P, H	significant decline of psoriasis severity score in 6 patients, minimal advantage in 1 patient, no advantage in 3 patients. Epidermal thinning and regenaration without sings of psoriasis	hypo- and hyper-pigmentation
arm/trunk	polysporine ointment, corticosteroid ointment group II intralesional and different pulse durations intralesional	no	E, S, I on 0-4 scale, P, H	significant clinical improvement; no significant difference between 0.45 and 1.5 ms; histological normalization after treatment	mild hyper-/ hypo-pigmentation
elbow/leg/ trunk	dermabrasion	emollient	ECR, P, H	3 (of 11) patients treated with laser showed complete remission vs 5 (of 6) treated with dermabrasion. Partial response in 6 laserpatients, and 2 patients showed no response. Histology in one patient was without characteristics of the disease.	slight hyper- and hypo-pigmentation
trunk/limbs	untreated lesions, salicylic acid and eximer laser	salicylic acid 1week before every treatment	PASI, PSI, P and spectrophotometric intracutaneous analysis	6 patients showed complete clearance, and 15 patients showed improvement. 9 patients had the same or better response compared to the excimer laser.	hypo-pigmentation and blistering
trunk/limbs	salicylic acid+ PDL and salicylic acid and clobetasol proprionate	no/salicylic acid before every treatment	modified PASI, P	mPASI decreased in all groups when compared with baseline, no statistically significant difference between PDL and PDL/salicylic acid.	mild to moderate hyper-pigmentation
hands/feet	no	calcipotriol or salicylic acid before each treatment	ECR, P	76% good to very good improvement. Average duration of remission 11 months	transient hyper- and hypo-pigmentation
trunk/limbs	vs calcipotriol/ betamethasone dipropionate	salicylic acid before initial treatment	E, I, S on 0-4 scale,P	significant difference in SUM score in favour of PDL. Pain scores declined although not statistically significant	hyper-pigmentation
unknown	vs UVB vsPDL + UVB vs no treatment	salicylic acid before each treatment	PGA-score	significant improvement in both PDL as UVB treatment. No significant differences between PDL-UVB; No synergism of both therapies is observed	transient hyper-pigmentation

Author	LOE	Study type	No. of patients	Laser parameters				Treatment parameters		
				λ	ø	pulse duration	fluence	No. of treatments	Treatment interval	Follow-up
Noborio *et al.*, 2009 (24)	4	CS	11	585	10	0.45	8.0	4.5 (1-9)	4w	1 m
Fernández-Guarino *et al.*, 2009 (25)	4	CS	14	595	7	6.0	9.0	6	4w	6 m
Oram *et al.*, 2010 (26)	4	CS	5	595	7	1.5	8.0-10.0	3	4w	3 m
Acne										
Seaton *et al.*, 2003 (34)	1b	RCT, double blind	41 (36 completed)	585	5	0.35	1.5 and 3.0	1	_	12 w
Orringer *et al.*, 2004 (35)	1b	RCT, single blind	40 (26 completed)	585	7	0.35	3.0	1(group1); 2(group 2)	0 (group 1, single treatment), 2 weeks (group 2)	12 w
Jasim. *et al.*, 2005 (36)	3b	OL, intrapatient)	10	595	10	6.0	7.0	1	_	6 w
Harto *et al.*, 2007 (37)	4	OL	36 (30 completed)	585	?	0.35	2.5	3	4w	12 w
Haedersdal *et al.*, 2008 (38)	4	intrapatient comparative trial	15 (12 completed)	595	10	10	7.5 (2 passes)	3	2w	12 w
Sami *et al.*, 2008 (39)	4	comparative study	15 (30 other patients were treated with IPL or LED)	585	7	0.35	3.0	4.1		
Jung *et al.*, 2009 (40)	4	Randomized prospective, double blind	18 (16 completed)	585	7	40	7.0	3	2w	12w
Leheta *et al.*, 2009 (41)	3b	randomized trial	15 (30 treated with topical treatment or chemical peels)	585	7	0.35	3.0	6	2w	8m

Location	Control side	Pre-treatment	Tool assessment	Results	Side effects
trunk/arm	no	7% lidocaine creme	E, S, T on 0-4 scale, H	significant decline in plaque severity score; significant decrease in microvessel count; downward trend in mean microvessel diameter	
nails	methylaminolaevulinic acid and PDL	no	NAPSI, P	a decrease in NAPSI for both treatments; No statistical difference between the treatmetn	
nails	no	no	NAPSI	significant decrease in NAPSI score	
face	parallel group	no	Leeds grading system (ref. 49) and lesions count	After 12 wks decline in acne severity (Leeds scale) 3.8 (SD1.5)to 1.9(1.5)in PDL and 3.6 (1.8)to 3.5 (1.9) in control group (p=0.007). Total lesions fell by 53% in PDL and 9% in controls (p=0.023). Inflammatory lesions fell by 49% in PDL and 10 % in controls (p=0.024). No differences between two fluence levels.	
face	yes	no	lesions count, P	No significant differences between laser treated vs untreated skin for reductions in mean papule counts (38% vs 25% p=0.08), mean pustules counts (0 vs 35 %, p=0.12)or mean comedone counts (9%vs 6%, p=0.63) No significant difference in overall acne severity between treated and untreated skin	post-inflammatory hyperpigmentation
face	yes, intra patient	no	modified Leeds Acne Score (ref 50), P	Significant reduction in the Modiefied Leeds Acne Score from 4.1 to 2.8 (treated site), from 3.7 to 3.5 (untreated site) (p<0.05)	
face	no	no	lesions count, P	Inflammatory lesions: reduction of 57 % after 12 weeks, non-inflammatoiry lesions: reduction of 27% after 12 weeks.	
face	MAL cream on one side of the face according to randomisation	no	lesions count, P	Inflammatory lesions were reduced more on MAL-LPDL treated than on LPDLtreated sides alone (wk 4: 70% vs 50%. P=0.03, wk12 80%vs67% p=0.04). non inflammatory lesions reduced similarly.	Erythema, edema and pustular eruption from MAL incubation.
face	no	no	ECR	> or = 90 %clearance of their inflammatoiry lesions was seen after 4.1 +/- 1.39 sessions in the PDL group; after 6.0 +/- 2.05 sessions in the IPL group and after 10.0 +/- 3.34 sessions in the LED group	
face	no, other side treated with PDL and Nd-YAG	no	Cunliffe's grading system (ref 52), lesions count, P,H	Significant reduction for inflammatory as well as for non-inflammatory acne lesions after both PDL and PDL/Nd-YAG. No significant difference between both treatments at the end of the study. Both treatments↓inflammation and IL-8 expression and↑TGF-β	no significant adverse reactions
face	no; other patients received either topical treatment	no	Leeds acne scoring system,P	Significant decrease in all three groups, no significant difference was detected between the three groups; remission in the follow-up period was significantly higher in the PDL group	

Author	LOE	Study type	No. of patients	Laser parameters				Treatment parameters		
				λ	ø	pulse duration	fluence	No. of treat-ments	Treatment interval	Follow-up
Choi *et al.*, 2009 (42)	4	split-face, single blind, RCT	20	585	10	40	8.0-10.0	4	2w	12w
Lupus erythematodes										
Nunez *et al.*, 1995 (53)	5	CR	1(SLE)	585	5	0.45	7.25-8.75	5		16
Nunez *et al.*, 1995 (54)	4	CS	4(SLE)	585	5	0.45	6.75-8.75	3-6		16
Maushagen-Schnaas *et al.*, 1997 (55)	5	CR	1 (CDLE)	585	7; 10		5.5 and 3.5	2	4w	12m
	5	CR	1 (SLE)	585	7; 10		5.5-6.0 and 3.2	3	1-5m	12m
Raulin *et al.*, 1999 (56)	4	CS	8 (CDLE)	585	5;7;10	0.45	3.4-7.0	3.8(1-9)	2w-5m	14.3 (5-32m)
	5	CR	1 (SCLE)	585	7	0.45	3.0-7.0	6	4w	inter-rupted
	4	CS	2 (SLE)	585	5;7	0.45	5.5-6.5	7.5 (7-8)	1-5m	3-6m
Gupta *et al.*, 1999 (57)	5	CR	1 (SCLE)	585	5	0.45	5.3	4	1m	
Baniandres *et al.*, 2003 (58)	4	CS	5 (SLE)	585/595	5;7	0.45-10.0	5.0-8 .75/6.0-12.0	3.8 (1-10)	2.8-12.0m	2.7y (8m-6y)
Erceg *et al.*, 2009 (59)	4	OL	12 (CDLE)	585	7	0.45	5.5	1-3	6w	6w
Diez *et al.*, 2011 (60)	4	OL	6(CDLE)	595	7	2	11	1	_	4w

Location	Control side	Pre-treatment	Tool assessment	Results	Side effects
face	no, IPL treatment on other half)	no	Cunliffe's grading system, lesions count, P,H	after 8 weeks inflammatoiry lesions were reduced to 14 % of baseline (vs 45 % in the IPL group); the non-inflammatoiry were reduced to 41% (PDL) and 57 % (IPL).Reduction of the acne grade from 2.5 to 1.0 (PDL) and from 2.5 to 1.2 (IPL). Patient satisfaction scores was 5.2 (PDL) and 4.7 (IPL). amelioration in inflammatory reactions and an increase in TGF-β expression after both treatments more prominent for PDL site	
face	no	no	ECR	exellent	
face	no	no	ECR, P, H	75 % clearance of the lesions; reduction in diameter of blood vessels. No changes in dermal infiltrate and direct immunofluorescence. (CR (ref 53) is included in this CS)	slight transient hyperpigmentation in one patient
cheek/back	no	no	ECR	complete clearance	
	no	no	ECR, H	complete clearance, decrease in IgG en C3	slight hyperpigmentation
face/thrunk	no	no	ECR, P	median 57.5 % clearance (varying from no visible improvement till total clearance) 1 patient was excluded due to concommitant *local* treatment	transient hyperpigmentation in 2 patients
	no	no	ECR, P	clearance rate 50%	
	no	no	ECR, P	75% clearance (70 and 80 %)	
face, neck and arms	no	no	ECR, P	marked improvement	
face, cheeks and thrunk	no	no	ECR, P, H	average clearance rate 68.0 % (range 50-80%);histology for lupus negative, IFD similar to pre-treatment biopsy. One patient with SLE, seven with CDLE and one with lupus tumidus were excluded due to concommitant *local* treatment	one patient developed hyper- and hypopigmentation
face, scalp, thrunk and limbs	no	no	modified CLASI, P	Baseline CLASI was 4.4 ± 0.2 (mean ± SEM), reaching 1.3 ± 0.3 after follow-up ($p<0.0001$). 'damage' CLASI did not show any significant change during and after therapy. The observed clinical improvement was confirmed by assessment of photographs taken before and after treatment by two additional independent observers	one patient developed slight hyperpigmentation
face, back, arm and hand	no	no	modified CLASI, H	Significant reduction of erythema and scaling after treatment; significant reduction of dermal lymphocytic infiltrate and an important reduction of basal damage. ICAM-1 and VCAM-1 expression was reduced	

Author	LOE	Study type	No. of patients	Laser parameters				Treatment parameters		
				λ	ø	pulse duration	fluence	No. of treat-ments	Treatment interval	Follow-up
Diez *et al.*, 2011 (60)	4	CS	2(Lupus tumidus)	595	7	2	11	1	_	4w
	5	CR	1(SCLE)	595	7	2	11	1	_	4w
Granuloma faciale										
Ammirati *et al.*, 1999 (62)	5	CR	1	585	5	0.45	8.0;8,5	2	2m	6y
Welsh *et al.*, 1999 (63)	5	CR	1(3 le-sions)	585	7	0.45	6.5-7.25	9		4m
				585	3	0.45	7.0-7.5			
				595	7	1.5	12.0	3	6w	
Elston, 2000 (64)	5	CR	1	595			6.5-7.0	3	1m	1m
Chatrath *et al.*, 2002 (65)	5	CR	1	595	7	3.0	9.5-12.0	3	6w	9m
Cheung *et al.*, 2004 (66)	4	CS	4	595	7	1.0-3.0	10.0-14.0	?	2-4m	
Fikrle *et al.*, 2011 (67)	4	CS	4	595	7	1.5	9.0-10.0	3-8	6-8w	6m
Leite *et al.*, 2011 (68)	5	CR	1	585		20	5.8-8.3	5		6m
Cutaneous sarcoidosis										
Goodman *et al.*, 1992 (69)	5	CR	1	585	5	0.46	5.0-8.0	2	7m	6m
Cliff *et al.*, 1999 (70)	5	CR	1	585	5	0.45	5.6-7.3	6	6w	2m
Ekbäck *et al.*, 2005 (71)	5	CR	1	585	?	0.45	6.75-7.0	10		
Holzman *et al.*, 2008 (72)	5	CR	1	595	7	0.5	7.6-7.8	3	6w	12m
Roos *et al.*, 2009 (73)	5	CR	1	585	12	0.5	6.0	1	_	4w

Location	Control side	Pre-treatment	Tool assessment	Results	Side effects
face and back	no	no	modiefied CLASI, H	Significant reduction of erythema and scaling after treatment; No epidermal change, no basal cel damage, decline of infiltrate in one patient. Significant decline of both ICAM-1 as VCAM-1	
face, back, arm and hand	no	no	modified CLASI, H	Abscence of erythema and scaling after treatment. No biopsie data available after treatment	
nose	no	no	ECR, P	persistent clinical eradication	
nose and cheek	no	no	ECR, P	complete remission in all lesions	mild epidermal atrophy
	no	no	ECR, P		
	no	no	ECR, P		
face	no	no	ECR, P	complete clearing	
nose	no	no	ECR, P	significant flattening of the lesions after two treatments, complete clearing after the third	
temporal, cheek, nose	no	no	ECR, P	two patients achieved a significant cosmetic improvement; the lesions remained unchanged in the other two patients	
face	no	no	ECR, P	complete flattening and bleaching in three patients (excellent), one lesion remained bright red-brown after treatment (very good)*(local steroid if no improvement after 2 sessions)*	
scalp	no	no	ECR, P	Marked improvement	
nose	no	no	ECR, P	improvement of 75 % after two treatments	
nose	no	no	ECR, P, H	considerable cosmetic improvement; presence of non-caseating granulomas in dermis; paucity of upper dermal blood vessels	
cheek		no	ECR, P	less reddish and somewhat thinner (after treatment with other laser there was a complete healing)*(twice frequenced-double YAG laser, after 10 PDL treatments)*	
cheek	no	no	ECR, P	clinical remission afer 3 treatments	
back	no	no	ECR, P	slight reddening, but the lesions had completely resolved	

Author	LOE	Study type	No. of patients	Laser parameters				Treatment parameters		
				λ	ø	pulse duration	fluence	No. of treat-ments	Treatment interval	Follow-up
Eczematous skin lesions										
Syed *et al.*, 2008 (76)	3b	OL	12	595	7		4.0;4.5;5.0	1	_	6w
Rosacea papulopustulosa										
Berg *et al.*, 2004 (88)	3b	OL	14 (10 completed the study)	585	5	0.5	5.75-7.75	2.4 (1-4)		10m
Bernstein *et al.*, 2008 (89)	4	CS	20 (17 completed the study)	595	3x10 12	40 3	17-19 6.0-7.0	4	4w	2m
Lichen sclerosis										
Rabinowitz *et al.*, 1993 (80)	5	CR	1	585	5		5.75-6.25	4		
Greve *et al.*, 1999 (81)	5	CR	1	585	7	0.3-0.45	5.3-6.0	4	4-6w	7m
Passerson *et al.*, 2009 (82)	5	CR	1 (2 le-sions)	595	10		10.0	2		1m
Granuloma annulare										
Sniezek *et al.*, 2005 (84)	5	CR	1	585	5	0.45	6.75	3	5m; 8m	3y
Slinger *et al.*, 2008 (85)	5	CR	1	595	7	1.5	8.0	1	_	36w
Jessner lymphocitic infiltration										
Borges da Costa *et al.*, 2009(86)	5	CR	1	595	10	0.5	8.0	1	_	?
Reticular erythematous mucinosis										
Greve *et al.*, 2001 (87)	4	CS	1	585	7	0.3-0.45	5.4-6.9	5	2.8m (2-7)	
			1	585	7		6.0	3	1m; 3m	2m

Location	Control side	Pre-treatment	Tool assessment	Results	Side effects
	no	no	Eczema Severity Score (ESS), VAS	A significant decrease in ESS and a significant difference in eczema severity assessed by VAS	one patient have a super-infection with *C.albicans* at the treated site
face	no	no	ECR	Markedly less (n=2), slight less (n=3), unchanged (n=3) worsened (n=2)	Hyper-pigmentation in five patients
face	no	no	ECR	Significant overall improvement	Slight pain and edema
genital	no	no	ECR	very good results	
neck/thrunk/ arm	no	no	ECR, H	complete clearance; no residu of LSA	
abdomen/ breast	methyl-aminolevulinic acid in breast lesion	no	ECR	moderate effect on abdominal lesion (PDL), marked improvement in breast lesion (PDL-PDT)	
wrist	no	no	ECR	reduction in erythema and almost complete flattening	
thrunk/limbs	no	no	ECR	complete flattening and lighting	slight transient hypo-pigmentation
limbs	no	no	ECR, H	complete clearing of all lesions; regression of histological findings	
chest/abdomen	no	no	ECR, H	only minimal residus visible; regulary structured skin without acute inflammation. No significant lymphocytic infiltrates or mucin deposits	
inframammary	no	no	ECR	skin almost completely healed	slight transient hypo-pigmentation

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General discussion and conclusions

5

General discussion and conclusions

In the general discussion and conclusions of the thesis, we will revisit the aims as defined in the introduction and formulate conclusions, based on the corresponding chapters of the thesis and relevant literature.

Aim 1: To investigate the efficacy of a vascular laser in spider naevi

Vascular lasers are considered the gold standard for the treatment of many vascular indications such as port-wine stains, hemangiomas and facial telangiectasias.[1,2] It is an effective method, however possible side effects restrict its use: pain, crust formation and pigmentary changes.[3,4] For smaller vascular lesions electrocoagulation (EC) is preferred by many dermatologists, as this method is easily available in daily practice and can be instantly performed in every out-patient department of the dermatologist and last but not least is well tolerated by the patients.

In **chapter 2.1** we compared the efficacy and safety of the vascular KTP laser with electrocoagulation in the treatment of spider nevi (SN). No significant difference between these methods was observed, although there was a tendency toward significance with respect to the clinical outcomes in favor of the KTP laser, both by patient assessments as by physician assessments. Pain was reported for both treatments, although for the KTP laser this was significantly less than for EC treatment. This can be explained by the lesser amount of tissue damage caused by laser treatment and the presence of a water cooled sapphire laser chill tip, causing some local anesthesia. Side effects such as hypopigmentation, hyperpigmentation or scar formation were not observed, making both KTP and EC suitable treatment options.
Conclusion: The vascular KTP laser cannot be regarded as superior to electrocoagulation for the treatment of spider nevi. If KTP is available at the treatment centre, this option may meet a higher patient satisfaction.

Aim 2: To explore the potential value of pulsed dye laser in solitary recalcitrant lesions of plaque psoriasis and CDLE

Studies in recalcitrant psoriasis

In psoriasis the presence of dilated, elongated and increased prominent superficial capillaries in the dermis can facilitate an increased influx of T-cells and other immunocytes into the skin, maintaining the chronic inflammatory reaction.[5,6] So far, the exact mechanisms behind the maintenance of the psoriatic inflammation remains unclear. Before the experiments of this thesis, several groups explored the potential value of PDL in psoriasis.[7-12] Variable results have been reported ranging

from no improvement at all to complete remission. The methods of pulsed dye laser (PDL) treatment were at variance with respect to fluence and spot size and pulse duration. Therefore, we set out a new study with a direct comparison of PDL with a commonly used therapeutic and we monitored the responses to treatment using clinical and immunohistological methods, in order to explore the potential and the mode of action of PDL in the treatment of psoriasis.

In **chapter 3.1** we evaluated the clinical efficacy and tolerability of PDL treatment compared to an active comparator: calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g ointment (CB) (Daivobet®/Dovobet®). After a dose finding a consistent schedule with fixed spotsizes and fluences and pulse duration was adhered to. The pulsed dye laser therapy showed an efficacy similar to the CB during the first 4 weeks of active treatment. However, PDL showed substantially and significantly higher efficacy after an additional 8 week follow-up. We have to reconcile that patients in this study had a history of refractory psoriasis not responding to topical therapies. Although PDL was well tolerated by most patients, one out of eight patients had to terminate the study early due to pain, which has been described as a possible side effect of this therapy. Another adverse event is the occurrence of pigmentary changes after treatment. Indeed, residual hyperpigmentation was observed in 4 out of 8 patients.
Conclusion: PDL treatment may be considered for the treatment of solitary recalcitrant psoriatic plaques, when other topical therapies have failed.

In **chapter 3.2** the immunohistological changes of PDL treatment were compared and contrasted with CB treatment. Histological studies to assess the effect of PDL have previously been performed, examining mostly the diseased dermal vasculature and angiogenesis. In one study, the mean microvessel count, using CD31 as marker, decreased significantly during PDL treatment and showed a strong positive correlation with the decrease of clinical severity.[13]. In another study, using indicators of angiogenesis, including endothelial surface area, endothelial cell proliferation and endothelial cell expression of adhesion molecules, showed that PDL affected the superficial capillary bed, causing a reduction in both endothelial surface area and endothelial cell proliferation in the superficial dermis.[14] Indeed, dermal capillary changes might be a permissive factor in the facilitation of traffic of pathogenic T-cells into the skin and in perpetuation of the psoriatic process. Therefore, we studied the dynamics of activated (CD2, CD25) and memory effector (CD45RO) T cells of the T-helper (CD4) and cytotoxic (CD8) subset and epidermal markers for proliferation (Ki67) and differentiation (K10) during PDL treatment in comparison with CB. Twelve weeks after initiation of PDL a significant decline of activated and memory effector T-helper cells in the dermis, cytotoxic T-cells in the epidermis and normalization of epidermal proliferation and keratinization in epidermal and dermal T-cell subsets was

seen, in contrast to the more modest changes following treatment with CB. We have to reconcile that these observations were made in chronic recalcitrant plaques. In the pathogenesis of psoriasis, evidence is accumulating that microvascular changes occur well before overt T-cell infiltration and epidermal hyperplasia in the process of formation of a psoriatic plaque. Therefore, it may be hypothesized that destroying the diseased capillaries helps preventing T-cells to extravasate into the skin. This might be a reason for long-standing therapeutic effect of PDL in psoriasis and the observed prolonged immuno-histochemical and clinical improvements.
Conclusion: Memory effector T-helper cells and cytotoxic T cells, as well as markers for epidermal proliferation and keratinization in recalcitrant psoriatic plaques are reduced by PDL treatment well beyond the effect of CB treatment.

Studies in recalcitrant CDLE

Untreated CDLE can lead to disfigurement in openly visible areas such as the face, scalp, neck and hands, resulting in major psychologic stress.[15,16] When current treatment options lack efficacy or adverse events are experienced, PDL treatment may be tried. Indeed, efficacy of PDL treatment has been claimed in several reports.[17-20] However the evidence for these claims is limited so far:

I. In none of these studies validated scoring methods were used.
II. Different laser parameters, different treatment schedules, and even different laser devices complicate the interpretation of these studies.

In **chapter 3.3** we described the development of a new scoring system for CDLE which focuses on one single representative target lesion: the DLE-skin score (DLE-SS) and the DLE-photo score (DLE-PS). The first one is the sum of erythema(E), induration(I), scaling(S) and atrophy(A),and the latter is the sum of erythema(E), scaling(S) and atrophy(A), because induration cannot be measured from a picture. Both DLE-SS and DLE-PS proved reliable methods in the assessment of a single CDLE lesion. The inter-observer variability of the DLE-PS was low, even lower than the intra-observer variability of the DLE-SS (2.0 vs 6.0). We also found a high correlation between the DLE-SS and DLE-PS. So, in conclusion, both DLE-SS and DLE-PS are reliable and easy-to-use methods to score disease activity in CDLE patients. We prefer, however, the DLE-SS because this method also measures induration, which is a key feature in disease activity.
Conclusion: DLE-SS and DLE-PS, as developed by our group, are reliable and easy-to-use methods to score one single lesion in CDLE patients (chapter 3.3). These scores do not provide a differentiation between disease activity and damage.

During the above mentioned studies a new scoring system was published: the cutaneous lupus erythematosus disease area and severity index (CLASI) which is

a validated instrument to measure disease severity and improvement in CDLE.[21] This score comprises the components erythema, induration, scaling and atrophy of the DLE-PS and DLE-SS. But it extends this score as it records and values the areas of involvement, based on an assessment of the actual sites of involvement and it differentiates between "disease activity" and "disease damage". The latter is of major importance in the evaluation of the effect of treatments. The CLASI is a good scoring system to investigate the value of a treatment for the management of the patient with DLE as disease activity and damage are scored separately. It was, however not developed to score one single target lesion.

In **chapter 3.4** we evaluated one single target lesion in 12 patients with recalcitrant CDLE during treatment with the PDL, using standardized laser parameters and treatment intervals. Instead of using the developed scoring system (3.3) we used the CLASI as this score differentiates between disease activity and damage. As we only assessed one target lesion in stead of the whole body, we decided to refer to this scoring system as the limited CLASI. We evaluated whether the CLASI scoring method was applicable to one single lesion. CLASI (disease-activity) comprises erythema, induration and scaling. CLASI (disease-damage) comprises dyspigmentation, scarring, and atrophy. The CLASI (disease-activity) and the CLASI (disease-damage) were calculated for each target lesion before and during laser treatment. At the same time clinical pictures of the target lesion were taken before and after treatment, and evaluated by two independent dermatologists using the CLASI. A significant decline in the limited CLASI (disease-activity) was observed after 6 weeks, after 12 weeks, and at follow-up. Baseline limited CLASI (disease-activity) was 4.4 ± 0.2 (mean ± SEM), reaching 1.3 ± 0.3 after follow-up (p <.0001). The limited CLASI (disease-damage) did not show any significant change during or after therapy. Therefore, it is important to differentiate between activity scores and damage scores also in the application of DLE-SS and DLE-PS. The observed clinical improvement was confirmed by two independent observers by clinical assessment of photographs (r =0.87 and r=.89; both p <.05). The two photograph observers intercorrelated well with r =0.96. Patients experienced minimal pain during treatment and only one patient developed slight hyperpigmentation. The overall cosmetic result was fair.

Conclusions:

I. The use of the CLASI scoring method was extended for the follow up of severity of one single CDLE lesion: the limited CLASI.
II. Limited CLASI (disease-activity) is an assessment tool which permits quantification of relevant clinical improvement in recalcitrant CDLE.
III. In the present study, limited CLASI was not superior to DLE SS, as disease damage did not change during treatment.

IV. PDL treatment is an effective and safe therapy for patients with refractory CDLE, and may be considered for treatment when topical and/or systemic therapies have failed or are contraindicated.

Aim 3: To position pulsed dye laser therapy in inflammatory skin diseases based on a systematic literature review

PDL has been used in various inflammatory skin conditions. Many reports are available and the outcomes are at variance. The methodology of PDL in various reports is often different. Therefore, we felt that it was important to get a clear view on the actually available evidence on the treatment of PDL in inflammatory skin diseases.

In **chapter 4.1** all publications of the treatment of inflammatory skin diseases with the pulsed dye laser from Januari 1992 till August 2011 were collected, and after determining the level of evidence according to the Oxford Center for Evidence-based Medicine Levels of Evidence, a recommendation grade was given for all found inflammatory skin disease. Literature concerning treatment efficacy and safety of pulsed dye laser for inflammatory skin diseases was diverse. Overall, most studies[22] have shown limitations in small patient numbers, inconsistent treatment parameters, non-validated treatment parameters and a relatively short follow up period. Large randomized controlled trials with consistent laser parameters, validated outcome measures and long follow-up period were lacking.
Psoriasis was the most frequently investigated inflammatory skin disease[22]. All studies described the treatment of localized psoriasis, which mostly concerned chronic, stable plaque psoriasis, sometimes explicitly described as recalcitrant, not responding to conventional therapy such as potent topical steroids, UVB, PUVA and tar. The results of the individual studies were at variance. Despite the frequency of this skin disease, no large randomized controlled trials on PDL for psoriasis were identified. Practically, PDL treatment should be restricted to a few psoriasis plaque lesions which are resistant to conventional therapy. Taking into consideration the evidence for superior efficacy in psoriasis as compared to topical treatment (present thesis) and various promising results as described in the review, according to our opinion, PDL should be considered for solitary recalcitrant psoriatic lesions.
Two large randomized controlled trials were preformed for acne treatment with PDL.[22] The results of these studies were at variance, which could be explained by different laser parameters which were used and other treatment regimens. PDL treatment for acne in other studies showed good results compared to a control side and compared to conventional treatments. Despite these positive finding it is still unclear, whether PDL treatment for acne will become a standard treatment in the future. No large intra-patient, left right comparative studies were done with PDL

treatment in comparison with other well established, easy accessible treatments. Therefore we cannot conclude that PDL has an added value to conventional forms of therapy. One could hypothesize that it can be an alternative when topical therapies have failed or are contraindicated, before starting systemic therapy. However, so far, a study showing the value of PDL in recalcitrant acne is not available to the best of our knowledge.

Evidence for other in the review mentioned inflammatory skin diseases (SLE, CDLE, SCLE, granuloma faciale, cutaneous sarcoidosis, chronic eczema, lichen sclerosis, granuloma annulare, Jessner lymphocytic infiltration of the skin, reticular erythematous mucinosis and papulopustular rosacea) is of a low level, i.e. grade C and D. While the incidence of these skin diseases, except for chronic eczema, is quite low, it is unlikely that large randomized trials will be performed in the near future to position the PDL for these skin diseases. Despite the low recommendation level, we recommend to consider treating recalcitrant lesions in these diseases with PDL as a last resort treatment, when topical and/or systemic therapies have failed or are contraindicated. In this respect we have to realize that unmet medical need in these patients can be substantial as these treatment resistant lesions are often located in the facial area and chest.

Conclusions:

I. Evidence grade B is allocated for PDL treatment of both localized psoriasis and acne vulgaris.
II. PDL has an added value in the treatment of recalcitrant psoriasis (present thesis).
III. For all other described inflammatory skin diseases PDL seems to be promising, although the level of recommendation did not exceed level C.
IV. Controlled studies, taking into consideration the long-term course of the disease in large groups of patients are needed.

Overall aim:

At the end of this thesis we revisit the overall aim: To explore the value of pulsed dye laser in the treatment of inflammatory skin diseases, inspired by the well established effect in vascular lesions and the evidence of involvement of the microvasculature in inflammatory dermatoses.

Indeed in classical vascular lesions, PDL has a well established position. But is it the panacea which makes this treatment first choice in all situations? In a common condition such as spider naevi, clearly, treatment by electrocoagulation remains to be an excellent first choice.

Reviewing the literature, one can conclude that our current understanding of vascular involvement in inflammation has expanded and several new leads to target the microvasculature in these diseases are promising research targets.

Validated scoring systems are crucial in order to be able to assess the value of treatments. In this thesis we have made a contribution to the development of new scoring systems in DLE.

Our investigation on the potential value of vascular lasers in inflammatory skin diseases comprised exploratory studies in solitary recalcitrant psoriasis plaques and recalcitrant DLE lesions and a systematic literature review. In both treatment resistant conditions, this thesis suggests that PDL is a valuable treatment option well beyond the efficacy of current anti-inflammatory treatments.

The evidence on efficacy and cost effectiveness of PDL in inflammatory skin diseases remains to be studied further, in order to position vascular lesions in S3 guidelines for the treatment of these diseases.

This thesis lends support for the development of new treatment options targeted on the microvasculature of inflammatory skin diseases.

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Summary & Samenvatting 6

Summary

The overall aim of the thesis is to explore the value of pulsed dye laser in the treatment of inflammatory skin diseases, inspired by the well established effect in vascular lesions and the evidence of involvement of the microvasculature in inflammatory dermatoses.

In classical vascular lesions, PDL has a well-established position. But is it the panacea that makes this treatment first choice in all vascular skin lesions? In **chapter 2.1** a comparative study between KTP laser and electrocoagulation was carried out. No significant difference between these methods was observed, although there was a tendency toward significance with respect to the clinical outcomes in favor of the KTP laser. Pain was reported for both treatments, although for the KTP laser this was significantly less than for EC treatment. KTP laser cannot be regarded as superior to electrocoagulation. If KTP is available at the treatment center, this option may meet a higher patient satisfaction.

In the treatment of inflammatory skin diseases an important unmet medical need exists for recalcitrant treatment resistant lesions. The question was addressed whether pulsed dye laser (PDL), by targeting the endothelial changes in these recalcitrant inflammatory lesions, might provide a unique last resort treatment for these therapy resistant lesions.

We explored the potential value of pulsed dye laser in inflammatory skin diseases:
In **chapters 3.1 and 3.2** our investigations in solitary recalcitrant psoriatic lesions have been described.
The clinical efficacy and tolerability of PDL treatment was compared with a first line topical treatment: calcipotriol 50 µg/g and betamethasone propionate 0.5 mg/g ointment (CB) (Daivobet®/Dovobet®). In view of its superior efficacy, PDL treatment may be considered for the treatment of localized, recalcitrant plaque psoriasis, when other topical therapies have failed.
The immune histological changes of PDL treatment were compared and contrasted with CB treatment: memory effector T-helper cells and cytotoxic T cells, as well as markers for epidermal proliferation and keratinization in recalcitrant psoriatic plaques are reduced by PDL treatment well beyond the effect of CB treatment.
In **chapter 3.3 and 3.4** the investigations in solitary recalcitrant CDLE lesions have been described.
Before starting therapeutic evaluations a new scoring system for CDLE was developed and evaluated by our group, which focuses on one single representative target lesion: the DLE-skin score (DLE-SS) and the DLE-photo score (DLE-PS). The first one is the sum

of erythema (E), induration (I), scaling (S) and atrophy (A), and the latter is the sum of erythema(E), scaling(S) and atrophy(A). DLE-SS and DLE-PS are reliable and easy-to-use methods to score one single lesion in CDLE patients. The score is comparable with the SUM score in psoriasis. This score is not providing a differentiation between "disease activity" and "disease damage" and it does not take into account the various localizations. During our studies another group published a new scoring system: The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI). CLASI comprises the key elements E, I, S and E of the DLE-SS and DLE-PS We used for our studies on the efficacy of PDL in CDLE the CLASI as it differentiates between disease activity and disease damage. As we did our studies on solitary lesions we designated the scoring system "limited CLASI". PDL treatment proved to be an effective and safe therapy for patients with refractory CDLE, and may be considered for treatment when topical and/or systemic therapies have failed or are contraindicated.
PDL has been used in various inflammatory skin conditions. Many reports are available and the outcomes are at variance. In **chapter 4.1** a systematic literature study has been described, analyzing all publications of the treatment of inflammatory skin diseases with the pulsed dye laser from January 1992 till August 2011. The following conclusions were drawn:

- *Evidence grade B is allocated for PDL treatment of both localized psoriasis and acne vulgaris.*
- *PDL has an added value in the treatment of recalcitrant psoriasis (present thesis).*
- *For various inflammatory skin diseases PDL seems to be promising, although the level of recommendation did not exceed level C.*
- *Controlled studies, taking into consideration the long-term course of the disease large groups of patients are needed.*

In solitary recalcitrant inflammatory skin diseases, PDL has proven to provide a valuable treatment option beyond the efficacy of current anti-inflammatory treatments. The evidence on efficacy and cost effectiveness of PDL in these diseases remains to be studied further, in order to position PDL in S3 guidelines for the treatment of these diseases.

This thesis lends support for the development of new treatment options targeted on the microvasculature of inflammatory skin diseases.

Samenvatting

Het doel van dit proefschrift is om de waarde van de pulsed dye laser te onderzoeken bij de behandeling van inflammatoire huidaandoeningen, geïnspireerd door het reeds bewezen effect bij vasculaire afwijkingen en het bewijs van betrokkenheid van microvasculatuur bij inflammatoire dermatosen.
De pulsed dye laser heeft inmiddels een belangrijke positie verworven bij de behandeling van klassieke vasculaire afwijkingen. Maar is dit de panacee, waardoor deze behandeling de eerste keus is voor alle vasculaire afwijkingen? In **hoofdstuk 2.1** werd een vergelijkend onderzoek uitgevoerd tussen de KTP laser en electrocoagulatie. Er werd geen significant verschil gezien tussen deze beide methoden, alhoewel er een tendens was tot significantie in het voordeel van de KTP laser. Bij beide behandelingen werd pijn gerapporteerd, alhoewel dit voor de behandeling met de KTP laser significant lager lag, dan voor electrocoagulatie. De KTP laser kon niet als superieur worden beschouwd ten opzichte van electrocoagulatie. Indien men in de praktijk de beschikking heeft tot de KTP laser, dan zou behandeling hiermee tot een hogere patiënt tevredenheid leiden.

Bij de behandeling van inflammatoire huidaandoeningen bestaat er een grote behoefte voor de behandeling van recalcitrante, therapieresistente afwijkingen. De vraag die gesteld werd was of pulsed dye laser, door zijn directe werking op endotheliale veranderingen in deze recalcitrante inflammatoire laesies, een unieke laatste behandelkans zou kunnen verschaffen voor de behandeling van deze therapieresistente huidafwijkingen.

We onderzochten de potentiële waarde van de pulsed dye laser (PDL) bij inflammatoire huidziekten:
In de **hoofdstukken 3.1 en 3.2** worden onze onderzoeken bij solitaire recalcitrante psoriasis beschreven.
De klinische effectiviteit en tolerabiliteit van de PDL behandeling werd vergeleken met een eerste lijns topicale behandeling: calcipotriol 50µg/g en betamethasone propionate 0.5 mg/g ointment (CB) (Daivobet®/Dovobet®). Gelet op zijn superieure effectiviteit, kan PDL behandeling worden overwogen voor de behandeling van gelokaliseerde, recalcitrante plaque psoriasis, nadat andere topicale behandelingen onvoldoende werkzaam zijn gebleken.
De immunohistologische veranderingen na PDL behandeling werden vergeleken en afgezet tegen CB behandeling: Afwijkende bevindingen in de recalcitrante psoriasis plaques met betrekking tot effector T-helper geheugen cellen en cytotoxische T cellen, evenals met betrekking tot markers voor epidermale proliferatie en keratinisatie worden minder na PDL behandeling, meer dan het effect van CB behandeling.

In de **hoofdstukken 3.3 en 3.4** worden onderzoeken naar solitaire recalcitante chronische discoide lupus erythematodes (CDLE) laesies en de meetmethoden hiervan beschreven.
Nog voor de aanvang van therapeutische evaluaties, werd een nieuw scoringssysteem voor CDLE ontwikkeld en geëvalueerd door onze groep, met de focus op een enkele "test" laesie: de DLE-skin score (DLE-SS) en DLE-photo score (DLE-PS). De eerste is een optelsom van erytheem (E), induratie (I) schilfering (S) en atrofie (A) en de laatste is de optelsom van erytheem (E), schilfering (S) en atrofie (A). DLE-SS en DLE-PS zijn betrouwbare en gemakkelijk bruikbare methoden om een enkele laesie in CDLE patiënten te scoren. De score is vergelijkbaar met de SUM score in psoriasis. Deze score voorziet niet in een holistische benadering, noch in de differentiatie tussen "ziekteactiviteit" en "ziekteschade" en voorziet niet een score voor ernst met betrekking tot verscheidene lokalisaties. Gedurende onze studies werd een nieuw scoringssysteem door een andere groep gepubliceerd: "The cutaneous lupus erythematodes disease and severity index" (CLASI). CLASI bevat de hoofdelementen E, I, S en E van de DLE-SS en DLE-PS. Het CLASI scoringssysteem geniet de voorkeur om de behandelwaarde te onderzoeken voor de behandeling van de patiënt met CDLE, daar het differentieert tussen ziekte activiteit en ziekte schade. Wij hebben de CLASI in studie naar de effectiviteit van de PDL voor CDLE gebruikt, en konden aantonen dat deze scoringsmethode, in een aangepaste vorm (limited CLASI) ook toepasbaar kon zijn op een solitaire laesie. PDL bleek een effectieve en veilige manier te zijn voor de behandeling van hardnekkige CDLE laesie, en kan overwogen worden indien topische en/of systemische therapie tekort schiet of gecontra-indiceerd is.

PDL werd in verscheidene inflammatoire huidziekten toegepast. Veel rapporten hieromtrent zijn beschikbaar en de uitkomsten zijn wisselend. In **hoofdstuk 4.1** word een systematische literatuurstudie beschreven, waarin alle publicaties van de behandeling van inflammatoire huidziekten tussen januari 1992 en augustus 2011 worden beschreven. De volgende conclusie konden hieruit getrokken worden:

- *Bewijskracht graad B is vastgesteld voor PDL behandeling van zowel gelokaliseerde psoriasis als van acne vulgaris.*
- *PDL heeft een toegevoegde waarde in de behandeling van recalcitrante psoriasis (huidig proefschrift).*
- *Voor diverse inflammatoire huidziekten lijkt PDL veelbelovend te zijn, alhoewel het niveau van aanbeveling level C niet ontstijgt.*
- *Gecontroleerde studies, met inachtneming van het lange-termijns beloop van de aandoening in grote patiëntengroepen zijn nodig.*

Bij solitaire recalcitrante inflammatoire huidziekten, heeft PDL bewezen een

waardevolle behandeloptie te zijn naast de doeltreffendheid van huidige anti-inflammatoire behandelingen. Het bewijs van efficiëntie en kosten effectiviteit van PDL in deze aandoening zou nog verder onderzocht moeten worden, voordat de PDL kan worden gepositioneerd in de S3 richtlijnen van deze aandoeningen.

Dit proefschrift ondersteunt de ontwikkeling van nieuwe behandelingen gericht op de microvasculatuur van inflammatoire huidziekten.

List of publications
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List of publications

Erceg A, de Jong EMJG, van de Kerkhof PCM, Seyger MMB
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Curriculum Vitae

Angelina Erceg werd op 19 mei 1972 geboren te Dongen. In 1990 behaalde zij het VWO diploma aan het Dr. Schaepmancollege te Dongen. Datzelfde jaar begon zij haar studie geneeskunde aan de Rijksuniversiteit Limburg te Maastricht. In 1996 werd gedurende enkele maanden een klinische stage gelopen in het lasercentrum van het Massechussetts General Hospital/ Harvard Medical School, Boston U.S.A. onder leiding van dr. J.M. Grevelink. In dezelfde periode verrichtte zij tevens wetenschappelijk onderzoek naar laserbehandelingen binnen de dermatologie aan het Wellman Institute of Photomedicine/ Harvard Medical School, Boston U.S.A. onder leiding van dr. C.C. Dierickx en dr. R.R. Anderson.

Na het behalen van het artsexamen in 1997, werkte zij achtereenvolgens een jaar als artsassistent algemene heelkunde in het Maasland Ziekenhuis te Sittard, een jaar als artsassistent allergologie en immunologie in de Klokkenberg te Breda, twee jaar als artsassistent interne geneeskunde in het Albert Schweitzer Ziekenhuis te Zwijndrecht/Dordrecht en nadien een jaar als artsassistent dermatologie in het Catharina ziekenhuis te Eindhoven.

In maart 2003 ving ze de opleiding tot dermatoloog aan in het Universitair Medisch Centrum St. Radboud te Nijmegen. Tijdens deze periode werd onder leiding van prof. dr. dr. P.C.M. van de Kerkhof, dr. M.M.B. Seijger en dr. E.M.G.J. de Jong de basis gelegd voor dit proefschrift. Vanaf 1 september 2007 is ze geregistreerd als dermatoloog en is ze als zodanig werkzaam in het Amphia ziekenhuis te Breda/Oosterhout.

Angelina is getrouwd met Alexander Barentsen en samen hebben ze een zoon, Kasper Luka en een dochter, Sophie.

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